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Towards functional nanomaterials: the synthesis and characterisation of [60]fullerenyl peptides

William C. Hawkins

University of Wollongong

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A thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

Department of Chemistry
University of Wollongong
Wollongong, AUSTRALIA
January, 2007
For Mum and Dad
Declaration

The work described in this thesis does not contain any material which has been accepted for the award of any degree or diploma in this or any other University and to the best of my knowledge and belief contains no material previously published by any other person, except where due reference has been acknowledged.

Bill C. Hawkins

January, 2007
Sections of the work described in this thesis have been reported in the following publications:


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- Thanks to my entire family for the support and general interest in my work.
- Thanks to Mum, Dad, Shane and Suellen for everything, I will be eternally grateful.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Aib</td>
<td>α-aminoisobutyric acid</td>
</tr>
<tr>
<td>Ala</td>
<td>alanine</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere(s)</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization (in mass spectrometry)</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from TMS</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>Da</td>
<td>Daltons</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact (in mass spectrometry)</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation (in mass spectrometry)</td>
</tr>
<tr>
<td>ESR</td>
<td>electron spin spectroscopy</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Molar equivalents</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-fluorenylethoxycarbonyl</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond coherence</td>
</tr>
<tr>
<td>HOAt</td>
<td>1-hydroxy-7-azabenzo triazole</td>
</tr>
<tr>
<td>HOBt</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
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</table>
$J$ coupling constant (in NMR)
L litre(s)
LUMO lowest unoccupied molecular orbital
µ micro
m multiplet (spectral), milli
M moles per litre
MALDI matrix assisted laser desorption ionisation (in mass spectrometry)
MHz megahertz
min minute(s)
mM millimoles per litre
MO molecular orbital
mol mole(s)
MS mass spectrometry
$m/z$ mass to charge ratio (in mass spectrometry)
NBS $N$-bromosuccinimide
NMR nuclear magnetic resonance
nOe nuclear Overhauser effect
NOESY nuclear Overhauser effect spectroscopy
Nu nucleophile
ppm parts per million (in NMR)
$p$-TsOH $para$-toluenesulfonic acid
q quartet (spectral)
$R_f$ retention factor (in chromatography)
RT room temperature
s singlet (spectral)
SET single electron transfer
$S_{N1}$ unimolecular nucleophilic substitution
$S_{N2}$ bimolecular nucleophilic substitution
t triplet (spectral)
TBDMS $tert$-butyldimethylsilyl
TFA trifluoroacetic acid
TfOH trifluoromethanesulfonic acid
THF tetrahydrofuran
TLC thin layer chromatography
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>TMS</td>
<td>trimethylsilyl, tetramethyilsilane</td>
</tr>
<tr>
<td>TOF</td>
<td>time of flight (in mass spectrometry)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>vis</td>
<td>visible</td>
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Abstract

Previous work within our group reported that the addition of \( N \)-
(diphenylmethylene)glycinate esters to [60]fullerene under Bingel conditions gave
methano[60]fullerenes. Likewise tethered bis-\( N \)-(diphenylmethylene)glycinate esters,
provided the corresponding bis-methano[60]fullerenyl iminoesters. Previous efforts to
deprotect the \( N \)-terminus and \( C \)-terminus of these methanofullerenes were unsuccessful,
however a novel reductive ring-opening of these compounds was discovered which
provided \( \alpha \)-fullerenyl glycinate derivatives.

Chapter 2 reports the structural re-assignment of the reaction products from the
addition of \( N \)-(diphenylmethylene)glycinate esters to [60]fullerene under Bingel
reaction conditions. The addition products were unequivocally assigned as
diphenylfullerenylidihydropyrroles rather than the previously reported methanofullerenyl
derivatives. Mechanistic details were proposed to account for the formation of the
[60]fullerenylidihydropyrroles and their reductive ring-opening products.

Reductive removal of the \( N \)-benzhydryl group of a ring-opened fullereryl
glycinate derivative provided ethyl \( \alpha \)-fullerenylglycinate, the first reported acyclic \( \alpha \-
substituted fullerenyl amino ester. Subsequent amide coupling to \( N \)-protected amino
acid chlorides provided fullerenylidipeptides. Preliminary results indicated that the Fmoc
protecting group can be removed from the \( N \)-terminus of a fullerenyl dipeptide under
basic conditions, and the resulting amine can be coupled to a \( N \)-protected amino acid
under standard EDCI/HOBt coupling conditions to deliver tripeptides “capped” with
fullerenylglycinate. Alternatively the \( t \)-butyl and ethyl [60]fullerenylidihydropyrroles
were shown to be readily converted to their corresponding carboxylic acids which then
could be coupled to ethyl L-phenylalaninate in good yield. Unfortunately all efforts to
ring-open the resultant fullerenylidihydropyrrole peptide were unsuccessful.
In Chapter 3, alternative iminoglycinates were examined in an effort to achieve a methanofullerene adduct from the Bingel reaction. Despite concluding that all iminoglycinates examined were unsuitable precursors for the generation of stable methano[60]fullerenyl derivatives, the reductive ring-opening of an unstable tert-butylidenemethano[60]fullerenyl derivative was achieved. Additionally, three new methods to generate fulleropyrrolidines from iminoglycinates were found, namely; intramolecular Mannich reaction, Mn(III) mediated radical addition and reduction of alkylfullerenylpyrroles. Importantly, a method for the generation of a stable, protected methanofullerenyl amino acid was discovered using α-bromophthylglycinate and the Bingel reaction.

Chapter 4 details the structural re-assignment of the reaction products from the addition of tethered bis-N-(diphenylmethylene)glycinate esters to [60]fullerene under Bingel reaction conditions. These reactions provided bis-diphenylfullerenylidihydropyrroles and not the previously reported bis-methanofullerenyl derivatives. The regiochemical outcomes however, remain as originally reported. The reductive ring-opening of tethered and non-tethered bis-adducts was achieved albeit in low yield. Intriguingly, only a portion of the expected isomers were observed.

Tether removal of the fullerenyldihydropyrroles to form fullerenyl bis-carboxylic acids and subsequent amide coupling to L-phenylalaninate esters delivered the first reported fullerenyl bis-peptides. Mono-transesterification of the trans-4 bis-adduct provided a key intermediate for the synthesis of tris-adducts, this was subsequently coupled to ethyl malonyl chloride, then subjected to Bingel cyclopropanation reaction conditions to afford two tris-adducts. However, the
regiochemistries were not determined as the overall reaction yields were poor and could not be further enhanced.

Chapter 5, details preliminary mechanistic investigations into the fragmentation of malonyl methano[60]fullerenes in the gas phase using ESI-MS and tandem MS.
# Table of Contents

1.1  [60]FULLERENE ...............................................................................................................................1  
1.2  \((C_{60-Ih})[5,6]FULLERENE STRUCTURE ..................................................................................1  
1.3  [60]FULLERENE REACTIVITY ........................................................................................................3  \n\begin{enumerate}  
\item 1.3.1 REDUCTION AND HYDROGENATION ................................................................................3  
\item 1.3.2 OXIDATION AND REACTION WITH ELECTROPHILES .................................................6  
\item 1.3.3 HALOGENATION ...............................................................................................................7  
\item 1.3.4 NUCLEOPHILIC ADDITIONS ...........................................................................................8  
\item 1.3.5 CYCLOADDITIONS .........................................................................................................10  
\item 1.3.6 RADICAL ADDITIONS ....................................................................................................12  
\end{enumerate}  
1.4  FULLERENYL AMINO ACIDS ....................................................................................................12  \n\begin{enumerate}  
\item 1.4.1 SYNTHESIS OF FULLERENYL AMINO ACIDS ................................................................13  
\item 1.4.2 FULLEROPROLINE THE FIRST TRUE FULLERENYL \(\alpha\)--AMINO ACID ...................16  
\end{enumerate}  
1.5  METHANO[60]FULLERENES ....................................................................................................20  \n\begin{enumerate}  
\item 1.5.1 CYCLOADDITION REACTIONS TO [60]FULLERENE ..................................................20  
\item 1.5.2 FORMATION OF METHANO[60]FULLERENES VIA ADDITION/ELIMINATION REACTIONS .................................................................................................................................23  
\end{enumerate}  
1.6  REGIOSELECTIVE ADDITION OF MULTIPLE ADDENDS TO [60]FULLERENE ......................27  
1.7  PROJECT AIMS ..........................................................................................................................29  
2.1  STRUCTURAL REASSIGNMENT OF THE ADDITION PRODUCTS OF DIPHENYLIMINOGLYCINATES TO [60]FULLERENE UNDER BINGEL CYCLOPROPANATION CONDITIONS .................................................32  \n\begin{enumerate}  
\item 2.1.1 A 2D-INADEQUATE STUDY OF DIPHENYLFULLERENYLDIHYDROPYRROLE 106A ........34  
\end{enumerate}  
2.2  REDUCTIVE RING-OPENING REACTIONS ..............................................................................39  \n\begin{enumerate}  
\item 2.2.1 OPTIMISATION OF THE REDUCTIVE RING-OPENING REACTION CONDITIONS ..........40  
\end{enumerate}  
2.3  FROM FULLERENYLDIHYDROPYRROLE DERIVATIVES TOWARDS FULLERENYL PEPTIDES .................................................................44  \n\begin{enumerate}  
\item 2.3.1 ETHYL [60]FULLERENYLGLYCINATE (PATH A) ............................................................45  
\item 2.3.2 INTRAMOLECULAR MANNICH REACTION WITH ETHYL FULLERENYLGLYCINATE ..........................47  
\item 2.3.3 AMINE COUPLING OF ETHYL FULLERENYLGLYCINATE (111) WITH AMINO ACIDS ....51  
\item 2.3.4 EXTENDING AMINE COUPLING TO PEPTIDES ..............................................................54  
\item 2.3.5 FMOC AMINO ACID CHLORIDES ...................................................................................56  
\item 2.3.6 ATTEMPTS AT LEWIS ACID MEDIATED CARBOXYL DEPROTECTION OF DIHYDROFULLERENYL DERIVATIVES 99 AND 123 .................................................................59  
\item 2.3.7 ATTEMPTS TO FORM FULLERENYLGLYCINE ................................................................61  
\item 2.3.8 CONCLUSIONS FOR PATH A .......................................................................................62  
\end{enumerate}  
2.4  FROM FULLERENYLDIHYDROPYRROLES 106A/B TO FULLERENYL PEPTIDES 110 (SYNTHETIC PATH B) .................................................................63
2.4.1 Fullerenyldihydopyrrole carboxylic acid .............................................. 64
2.4.2 Amide coupling of carboxylic acid 114 ................................................... 66
2.4.3 Attempted addition of diphenyliminopeptides to fullerene under Bingel conditions ........................................................................................................ 67
2.4.4 Attempted reductive ring-opening reactions on fullereny peptide 115 and fullereny acid 114 ........................................................................................................ 68

2.5 CONCLUSIONS ............................................................................................ 70

3.1 GENERATING METHANO[60]FULLERENYL DERIVATIVES FROM THE ADDITION OF IMINOGLYCINATES TO FULLERENE ........................................ 72

3.2 ALKYL IMINOGLYCINATES ...................................................................... 73

3.2.1 Synthesis of ethyl N-(2,2-dimethylpropylidene)glycinate ................. 74
3.2.2 Synthesis of ethyl N-(2,2',4,4'-tetramethylpentylidene)glycinate......... 74
3.2.3 Synthesis of camphor iminoglycinates ..................................................... 76

3.3 THIOIMINOGLYCINATES .......................................................................... 77

3.3.1 Synthesis ethyl and tert-butyl dithiomethylglycinate .............................. 77
3.3.2 Synthesis of dithiocyclohexylimine ......................................................... 78

3.4 AROMATIC IMINOGLYCINATES ................................................................. 80

3.4.1 Synthesis of ethyl benzylideneglycinate ................................................... 80

3.5 BINGEL CYCLOPROPANATION REACTION CONDITIONS .................... 80

3.5.1 Addition of ethyl N-(2,2-dimethylpropylidene)glycinate to [60]fullerene under Bingel conditions ................................................ 81

3.5.1.1 Manipulating the reaction conditions to alter product outcome........ 89
3.5.2 Addition of ethyl N-(2,2',4,4'-tetramethylpentylidene)glycinate to [60]fullerene under Bingel cyclopropagation reaction conditions .......... 91
3.5.3 Bingel cyclopropagation addition of tert-butyl camphoriminoglycinate to fullerene ................................................................. 95
3.5.4 Dithioiminoglycinate addition to C60 ....................................................... 97
3.5.5 Addition of dithiocyclohexylimine to [60]fullerene under Bingel cyclopropagation reaction conditions ................................. 98
3.5.6 Synthesis of ethyl benzylideneglycinate and the addition to fullerene under Bingel cyclopropagation conditions ........................................ 98

3.6 EXAMINATION OF THE BINGEL CYCLOPROPANATION REACTION CONDITIONS ................................................................. 100

3.7 SUMMARY/CONCLUSIONS ...................................................................... 103

3.8 REDUCTIVE RING-OPENING REACTION ON A MIXTURE OF 147 AND 148 ............................................................................................... 103

3.9 MANGANESE(III) MEDIATED RADICAL ADDITIONS TO FULLERENE ................................................................................................................... 108

3.9.1 Addition of alkyliminoglycinates (138-140) to C60 under Mn(III) induced radical conditions ................................................... 109
3.9.2 Manganese(III) mediated addition of thioiminoglycinates (143-144) to C60 ........................................................................................................ 112
3.9.3 **Manganese(III) mediated radical addition of ethyl benzyldenedeglycinate to C₆₀**

3.10 **FURTHER INVESTIGATION INTO THE MANGANESE(III) MEDIATED RADICAL ADDITION OF N-PROTECTED AMINO ACIDS TO FULLERENE**

3.11 **SUMMARY/CONCLUSIONS**

3.12 **ALTERNATIVE N-PROTECTED AMINO ESTER FOR BINGEL CYCLOPROPANATION ADDITION TO FULLERENE**

3.12.1 **Synthesis and bromination of phthalimides**

3.12.2 **Bingel cyclopropanation of 179 to [60]fullerene**

3.12.3 **Future directions**

3.13 **CONCLUSIONS**

4.1 **MULTIFUNCTIONALISED [60]FULLERENE DERIVATIVES**

4.2 **BIS-SUBSTITUTED [60]FULLERENE DERIVATIVES**

4.2.1 **Regioisomerism**

4.2.2 **Controlling regiochemical outcome**

4.3 **STRUCTURAL REASSIGNMENT OF TETHERED DIPHENYLIMINO BIS-ADDITIONS TO [60]FULLERENE**

4.3.1 **Changing the regioisomeric ratio for the addition of tethered diphenylimino bis-addends to [60]fullerene**

4.3.2 **Altering product outcome**

4.4 **TOWARDS MULTIFUNCTIONALISED FULLERENYL DERIVATIVES**

4.4.1 **Reductive ring-opening of fullerényl bis-adducts**

4.4.1.1 **Conclusions**

4.4.2 **[60]FULLERENYL BISPEPTIDES**

4.4.2.1 **Reductive ring-opening of bispeptide 204**

4.4.3 **Towards tris-substituted fullerényl derivatives**

4.4.4 **Regio and stereochemical evaluation of a base assisted cycloaddition of a tethered iminoglycinato to [60]fullerene**

4.5 **FUTURE DIRECTIONS AND CONCLUSIONS**

5.1 **[60]FULLERENE AND MASS SPECTROMETRY**

5.2 **METHANO[60]FULLERENE**

6.1 **CONCLUSIONS**

6.2 **FUTURE DIRECTIONS**

7. **EXPERIMENTAL**

8. **REFERENCES**

APPENDIX
1.1 [60]Fullerene

In 1985 investigations into the behaviour of pure carbon clusters by mass spectrometry led to the observation that when graphite was subjected to the pulsed nozzle/laser vaporization technique, the mass spectrum would show an extremely intense peak at \( m/z \) 720 assigned as \( \text{C}_{60} \). The structure of \( \text{C}_{60} \) was hypothesised to be a truncated icosahedral cage in which all the carbon atoms were connected by \( \text{sp}^2 \) bonds (Figure 1.1). This structure was termed buckminsterfullerene, named after the architect Buckminster Fuller whose giant icosahedral structures resembled the proposed structure. The next stable homologue is the football-shaped \( \text{C}_{70} \) ([70]fullerene) followed by a range of higher fullerenes (e.g. \( \text{C}_{76}, \text{C}_{78}, \text{C}_{82}, \text{C}_{84} \)). In 1990 a method was developed allowing for the macroscopic production of \( \text{C}_{60} \), and higher ordered fullerenes albeit in proportionally small yield, thus paving the way for further structural and reactivity examinations.

![Figure 1.1: Space filling model and a chemical structure diagram of [60]fullerene.](image)

1.2 \( (\text{C}_{60}-I_h)[5,6] \) Fullerene structure

The name \( (\text{C}_{60}-I_h)[5,6] \) fullerene provides structural information with the parenthetical prefix denoting the number of carbon atoms and the point group symbol, respectively. The numbers 5 and 6 denote that \( \text{C}_{60} \) is comprised of pentagons and
hexagons. There are 1812 possible structures for \( C_{60} \), however, as only one stable isomer exists for \((C_{60}I_h)[5,6]\) fullerene, the name can be simplified to \([60]\) fullerene. This stable isomer is the only one which obeys the isolated pentagon rule which states, “stabilised fullerene structures are formed when all pentagons are isolated by hexagons. Destabilised fullerene structures are formed by the presence of adjacent pentagons.”

Another structural feature of \([60]\) fullerene, and indeed all fullerenes, is the alternating bond lengths with those joining two hexagons (6,6-bonds) measuring 1.38 Å whereas those between a pentagon and a hexagon (5,6-bonds) were determined to be 1.45 Å.

In order to unambiguously describe \([60]\) fullerene derivatives, a set of rules for the numbering of carbon within the cage has been developed and is shown in Figure 1.2 below. The Schelgel diagram is a 2-D representation of the \( C_{60} \) cage, with the numbering shown as reported in the literature, and endorsed by the IUPAC.

![Figure 1.2: Chemical structure and Schlegel diagrams of \([60]\) fullerene; double bonds have been omitted for clarity, adapted from Thilgen et al.](image)

The numbering of the \([60]\) fullerene cage begins at the end of a contiguous helical pathway, with the corresponding axis called the reference axis. This allows for discrimination between inherently chiral fullerenes with absolute configuration...
stereodescriptors \((C)\) and \((A)\) where \(f = \text{fullerene}; C = \text{clockwise and } A = \text{anti-clockwise.}\)

The overall [60]fullerene structure can be imagined as fused cyclohexatrienes and [5]radialenes, which chemically has similar reactivity to an electron deficient alkene with localised double bonds. The primary driving force for addition to the fullerene cage is the relief of strain, by altering the hybridisation of the reacting fullerene carbon atoms from trigonal \(sp^2\) hybridisation, to the less strained tetrahedral \(sp^3\) configuration.\(^{10}\)

1.3 [60]Fullerene reactivity

The chemistry to functionalise [60]fullerene is presented below and has been divided into subgroups according to reaction type. These reactions include reduction, hydrogenation, oxidation, halogenation, cycloadditions, nucleophilic and radical addition reactions.

1.3.1 Reduction and hydrogenation

The first chemical transformations carried out with C\(_{60}\) were reductions, due to theoretical calculations of the molecular orbital levels of C\(_{60}\) which predicted that the lowest unoccupied molecular orbitals (LUMO) and the (LUMO + 1) had comparatively low energy and were triply degenerate.\(^{11-16}\) This indicated that C\(_{60}\) was a electronegative molecule, being reducible up to the hexaanion.\(^{17}\) This was confirmed with cyclic voltammetry studies, which showed the process to be reversible at slow scan rates (100 mVs\(^{-1}\)) with all reductions being one-electron transfer processes (Figure 1.3).\(^{17-21}\)
The controlled electrochemical reduction of [60]fullerene followed by quenching with electrophiles, such as alkyl halides, has produced the corresponding organodihydrofullerenes in good to moderate yield.\textsuperscript{22-24} As an example, a solution of C\textsubscript{60} in benzonitrile was electrolysed in the presence of tetra-\textit{n}-butylammonium perchlorate in a dry box, to afford a dark red solution of the C\textsubscript{60}\textsuperscript{2-} dianion. Treatment of this solution with a large excess of methyl iodide delivered the dihydrofullerene 1 as a 7 : 5 mixture of the 1,9 (\textbf{1a}) and 1,7 (\textbf{1b}) isomers, respectively (Scheme 1.1). Increasing the steric bulk of the electrophile was found to lead to the exclusive formation of the 1,7 isomer.\textsuperscript{23}

\textbf{Figure 1.3}: Reduction of [60]fullerene in MeCN/toluene at −10 °C using (a) cyclic voltammetry and (b) differential pulse voltammetry.\textsuperscript{18}
Chapter 1: Introduction

**Scheme 1.1**: Electrochemical reduction followed by methyl iodide treatment provided isomers 1a and 1b.

Reduction of C\textsubscript{60} can be achieved using various alkali metals including lithium\textsuperscript{25} and potassium.\textsuperscript{26} The 1,9-dihydrofullerene 3 was synthesised by the addition of potassium metal to a solution of [60]fullerene in 1-methylnaphthalene and THF to produce the dianion 2, followed by the addition of a large excess of benzyl chloride and quenching with acetic acid provided 3 in 64% yield (Scheme 1.2).\textsuperscript{26}

**Scheme 1.2**: Alkali metal reduction of fullerene followed by a benzyl chloride/acetic acid quench delivered 3.

Hydrogenation of [60]fullerene can be achieved using several procedures, perhaps most easily by direct hydrogenation with hydrogen gas under high temperature and pressure. The highest level of saturation achieved so far is C\textsubscript{60}H\textsubscript{48},\textsuperscript{27} however, the level of hydrogenation can be readily controlled by changing the hydrogen gas pressure and temperature. For example, at 400 °C and 80 atm. of H\textsubscript{2} the major product is C\textsubscript{60}H\textsubscript{18}.\textsuperscript{27} When C\textsubscript{60} was exposed to Birch reduction conditions (Li/NH\textsubscript{3}/t-BuOH) a mixture of C\textsubscript{60}H\textsubscript{36} and C\textsubscript{60}H\textsubscript{18} was produced.\textsuperscript{28} Interestingly, upon treatment of a
solution of $C_{60}H_{36}$ and $C_{60}H_{18}$ in toluene with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), pristine [60]fullerene was regenerated.28

1.3.2 Oxidation and reaction with electrophiles

Despite the oxidation of [60]fullerene being comparatively harder than its reduction,17 several oxidative functionalisation, as well as, electrophilic additions have been achieved. The epoxide 4 was generated by photooxygenation of $C_{60}$ in benzene (Scheme 1.3), with the likely mechanism being via the addition of singlet oxygen.29

![Scheme 1.3: Photolysis of fullerene in the presence of oxygen provided 4.](image)

The first fullereny1 derivative characterised by X-ray crystallographic analysis was the osmylated monoadduct 5,30 which was accessed by treatment of a solution of $C_{60}$ with osmium tetroxide (1 equiv.) and pyridine (2 equiv.). The complex 5 has also been fully characterised by analysis of its 2D-INADEQUATE spectrum (Scheme 1.4).31 When 5 was heated under vacuum, pristine [60]fullerene was returned.

![Scheme 1.4: Treatment of fullerene with osmium tetroxide afforded 5.](image)
1.3.3 Halogenation

The direct fluorination of [60]fullerene has been achieved using F$_2$ and by varying the temperature, pressure and reaction time, the level of fluorination can be somewhat controlled.$^{27,32}$ The highest stable level of fluorination achieved is C$_{60}$F$_{48}$ (6) (Scheme 1.5).$^{32,33}$ The precise structure of 6 has been determined by $^{19}$F NMR and X-ray crystallographic analysis.$^{34,35}$

![Scheme 1.5: Direct fluorination of fullerene](image)

The less stable chlorofullerenes have also been synthesised, with treatment of a solution of [60]fullerene in benzene with an excess of ICl at RT providing the isomerically pure C$_{60}$Cl$_{6}$ (7) (Scheme 1.6).$^{36}$ Other chlorination reagents include ICl$_3$ and KICl$_4$, which under varying conditions gave rise to C$_{60}$Cl$_n$ where $n$ = 8, 10, 12, 14, 26.$^{37}$ However these compounds were characterised as mixtures. Notably 7 can be dechlorinated to return C$_{60}$ either by heating to 400 °C,$^{38}$ treating with triphenylphosphine or by electrochemical reduction.$^{39}$

![Scheme 1.6: Direct chlorination of fullerene](image)

Bromination of [60]fullerene with Br$_2$ provides either C$_{60}$Br$_{24}$, C$_{60}$Br$_{8}$ or C$_{60}$Br$_{6}$ (isostructural with C$_{60}$Cl$_{6}$, 7) depending on the solvent used (Scheme 1.7).$^{40,41}$ The solvent dependency on reaction outcome has been attributed to the solubility profile of the resultant bromofullerene. Notably, all bromofullerenes mentioned here have been
characterised by X-ray crystallographic analysis. As seen with the chlorofullerenes, the bromofullerenes are temperature sensitive, and at high temperatures revert back to pristine [60]fullerene.

\[ \text{C}_60 \xrightarrow{150 \, ^\circ\text{C}} \text{C}_{60}\text{Br}_{24} \xrightarrow{\text{Br}_2} \text{C}_{60} \xrightarrow{\text{Br}_2, \text{CS}_2, 80\%} \text{C}_{60}\text{Br}_8 \]

\[ \text{Br}_2, \text{CCl}_4 \] \[ 92\% \]

\[ \text{C}_{60}\text{Br}_6 \]

**Scheme 1.7:** Direct bromination of fullerene.

### 1.3.4 Nucleophilic additions

The electron deficient [60]fullerene readily reacts with carbon nucleophiles (e.g. Grignard and organolithium reagents) to form various phenyl, alkynyl and alkylated derivatives. The synthesis of the first acetylene[60]fullerene derivative 8 was independently reported simultaneously by two groups (Scheme 1.8).

\[ \text{Li} \xrightarrow{\text{C}_{60}, \text{Toluene}, 110 \, ^\circ\text{C}} \text{H}^+ \]

\[ 45\% \]

**Scheme 1.8:** Reaction of fullerene with organolithium reagents delivers dihydrofullerenyl derivative.
Further studies on this acetylene system showed that quenching the lithium adduct with formaldehyde provided the alcohol 9 which could be treated with p-toluenesulfonyl chloride to afford the tosyl adduct 10 or alternatively, oxidised to provide the aldehyde 11 (Scheme 1.8).\(^{47}\) Other lithium acetylides have also been attached to C\(_{60}\), and various electrophiles used to react with the subsequent Li-fulleride.\(^{47-49}\)

It is well documented that primary and secondary amines readily undergo nucleophilic additions to the electron deficient [60]fullerene,\(^{50-52}\) while tertiary aliphatic amines have been shown to undergo photocycloadditions to [60]fullerene (Scheme 1.9).\(^{53}\)

![Scheme 1.9: Amines readily add to the fullerene spheroid.](image)

The precise mechanism of addition of amine derivatives to [60]fullerene is still under debate.\(^{54}\) Recently the bisadduct 12 was synthesised by treatment of a solution of C\(_{60}\) in air saturated chlorobenzene with an excess of \(N,N'\)-dimethyl-1,3-diaminopropane (Scheme 1.10).\(^{55}\) It was also reported that 12 was not formed in the absence of either light or air, suggesting that a singlet oxygen path with the addition of amine radicals to C\(_{60}\) was involved.\(^{54, 55}\) Conversely, the presence of oxygen in the addition of piperazine
to C_{60} was found to have a detrimental effect in the generation of 13, thus the likely mechanism for this reaction involved single electron transfer from the amine to the carbon spheroid.\textsuperscript{54}

![Scheme 1.10: Treatment of N,N'-dimethyl-1,3-diaminopropane and piperazine with fullerene provided 12 and 13, respectively.]

1.3.5 Cycloadditions

Of all [60]fullerene reactions, cycloadditions are the most studied. This is mainly due to the relative ease in producing mono-adducts, and the ability of C_{60} to act as a 2π electron deficient dienophile or dipolarophile. Scheme 1.11 displays some of the commonly used cycloaddition reactions, with the products typically used as intermediates in further reactions.
Chapter 1: Introduction

Scheme 1.11: Fullerene readily acts as a $2\pi$ electron deficient dienophile or dipolarophile.

When potassium cyanide powder was added to $C_{60}$ and vigorously vibrated in a high speed vibration mill (HSVM) a [2+2]-cycloaddition between two $C_{60}$ molecules occurred, exclusively forming the bis-adduct 14 (Scheme 1.12). When the reaction was done in solution, nucleophilic addition of the cyanide anion to $C_{60}$ occurred, which after an acid quench provided the dihydrofullerene 15.

Scheme 1.12: Treatment of fullerene with cyanide under HSVM and nucleophilic reaction conditions provided different fullerrenyl derivatives.
1.3.6 Radical additions

The tert-butylC\textsubscript{60} radical 16 has been generated by the photolysis of a solution containing [60]fullerene and either tert-butyl bromide, pivaldehyde, di-tert-butyl ketone, or by reaction of [60]fullerene with di-tert-butylmercury (Scheme 1.13).\textsuperscript{58, 59} ESR studies on 16 revealed delocalisation of the radical to the 2-, 4-, and 6-positions, with the highest spin density at position 2.\textsuperscript{59}

\begin{equation}
\text{ROOR} \rightarrow 2 \text{RO}^\bullet + \text{RH} \rightarrow \text{R}^\bullet + \text{C}_{60} \rightarrow \text{16 R = 'Bu}
\end{equation}

Scheme 1.13: Radicals readily add to the fullerene cage.

1.4 Fullerenyl amino acids

A large portion of synthetic [60]fullerene chemistry is directed towards providing biologically active substrates.\textsuperscript{60-65} The impetus for such work was to exploit the physical properties of [60]fullerene (such as sensitisation of singlet oxygen and electron acceptor characteristics) and combine this with the properties of biomolecules (water solubility and precise secondary and tertiary structure).\textsuperscript{17, 64, 66-68} For example, [60]fullerene derivatives covalently linked to peptides and proteins has been the goal of a number of research groups concerned with the application of [60]fullerene-peptide conjugates to biological problems.\textsuperscript{60, 65, 69-74} It was anticipated that the addition of biologically active compounds to [60]fullerene in a strict regioselective fashion would aid the activity and specificity of future therapies. The following section reports current progress in the synthesis of fullerenyl amino acids and related derivatives.
1.4.1 Synthesis of fullerenyl amino acids

From a materials science and medicinal chemistry perspective, fullerenyl amino acids are important targets potentially serving as central hubs in architecturally defined nanostructures or 3D-templates in drug design.\textsuperscript{62, 63, 67, 75-83} To date fullerenyl amino acids and peptide derivatives have been prepared by the initial attachment of a handle to fullerene followed by coupling to a protected amino acid or peptide.\textsuperscript{64, 71, 84-86}

The thermal addition of the diazomethane derivative 17 to C\textsubscript{60} and subsequent deprotection of the ester 18 provided the acid 19.\textsuperscript{87} This represented the first synthesis of a fullerenyl compound which had a synthetic handle to readily allow for peptide functionalisation (Scheme 1.14). The acid 19 was converted to the reactive acid chloride 20 which underwent amide coupling with the pentapeptide 21 under basic conditions to provide the first reported fullerenyl peptide 22.\textsuperscript{87}

\textbf{Scheme 1.14:} Synthesis of 22 through a diazo-addition of 17 to fullerene.
This work was extended to alkyl diazoacetates of the type 23, which were added to C_{60} forming the methano[60]fullerene 24, which was deprotected to the carboxylic acid 25 then coupled to amino acids under standard DCC coupling conditions to form fullerenyl amino acids e.g. 26a (Scheme 1.15).^{88, 89} Alternatively, a more efficient route was developed and allowed the direct addition of diazoamides to C_{60}. For example, a solution of [60]fullerene in toluene was treated with the diazoamide 27 at reflux for 48 h providing the fullerenyl amino acid 26b (Scheme 1.15).

![Scheme 1.15: Synthesis of 27 through a diazo-addition of 23 to fullerene.](image)

The [4+2]-cycloaddition of the silyloxy-butadiene 28 to [60]fullerene provided the ketone 29, after hydrolysis. Subsequent reduction with DIBAL–H afforded the racemic alcohol 30, a versatile synthon for the generation of fullerenyl amino acids
(Scheme 1.16). DCC mediated esterification of **30** with alanine and glutamate derivatives provided the fullerenyl amino acids **31-32**.\(^{21}\)

**Scheme 1.16**: Synthesis of fullerenyl amino acids **31** and **32**.

More recently **29** has been used to synthesise [60]fullerene substituted phenylalanine derivatives (Scheme 1.17).\(^{72}\) The amine substituted protected phenylalanine derivatives **33** were shown to readily undergo condensations reactions with **29** forming the analogous imine **34**, which were converted to the corresponding amine **35** by borane reduction. Treatment of the methyl glycinate derivative of **35** (R’ = OMe, R’’ = Me) with BBr\(_3\) led to the isolation of the free glycine analog **36**. While the N-Boc-glycine derivative of **35** (R’ = OH, R’’ = O'Bu) was coupled to ethyl glycinate under HBTU mediated coupling conditions to provide the peptide **37**.
**1.4.2 Fulleroproline the first true fullerenyl α–amino acid**

The [60]fullereneyl derivatives discussed in Section 1.4.1 are examples of fullerenyl amino acids. However none of these compounds mimic the structure of the majority of natural amino acids, which possess the general structure 38, where R is an alkyl or aryl side-chain (Scheme 1.18).

**Scheme 1.17:** Synthesis of fullerenyl amino acids 36 and 37: i- R’ = OMe, R’’ = Me, BBr3/HCl, CH2Cl2, ii- R’ = OH, R’’ = O’Bu, ethyl glycinate, HBTU, NEt3.

**Scheme 1.18:** The general structure of naturally occurring amino acids.
The first synthesis of an α-substituted fullerenyl amino acid, fulleroprolines (Fpr) was achieved by the addition of azomethine ylides to [60]fullerene.\textsuperscript{90-92} The azomethine ylide intermediates can be generated in two different ways, either \textit{via} a thermal ring-opening of aziridines (41) or \textit{via} tautomerisation of iminium salts formed by the condensation of α-amino esters (39) with aldehydes (40) (Scheme 1.19). These reactions allow for a significant number of Fpr derivatives to be generated by using different combinations of aldehydes and amino esters.

\textbf{Scheme 1.19}: The synthesis of fulleropyrrolidines can achieved by thermal addition of iminium salts or aziridine to fullerene.

Fpr analogs can be prepared with the pyrrolidine nitrogen protected (Scheme 1.20) or unprotected (Scheme 1.21).\textsuperscript{69} Addition of the aziridine 43 to [60]fullerene under thermal conditions formed the fulleropyrrolidine 44, subsequent treatment with TFA provided the secondary amine 45, which could then be acylated with acetic anhydride to provide 46 (Scheme 1.20).\textsuperscript{69}
Scheme 1.20: Synthesis of 46 was achieved through thermal addition of aziridine 43 to fullerene.

To obtain more useful Fpr derivatives for peptide synthesis the glycinate esters 47 and 48, and paraformaldehyde were added to C₆₀ to generate the free amines 49 and 50, respectively. These were relatively unstable and had to be kept as dilute solutions in the dark. 50, 69 However, the amine group was readily functionalised using standard acylation procedures with acid anhydrides and acid chlorides (Scheme 1.21), to deliver racemic fullerenyl amino esters like 51. Alternatively the amine 49 was protected as the N-Fmoc derivative 52, and then the tert-butyl ester converted to the acid 53 by treatment with TFA. Subsequent coupling with ethyl L-alaninate under EDCI/HOAt conditions afforded the diastereomers 54 and 55. The diastereomic ratio of 51 was determined by formation of the dioxopiperazines 56 and 57, thus eliminating the additional complexity in characterisation imposed by amide rotamers. 69
Scheme 1.21: Synthesis of peptides containing Fpr.
1.5 Methano[60]fullerenes

One of the most utilised [60]fullerene derivatives is the methano- or cyclopropyl-[60]fullerene. Their synthetic accessibility, structural diversity, conformational rigidity and the fact that [60]fullerene still retains most of its original properties has made this method of attaching functional groups attractive. The synthetic methods available to generate methano[60]fullerenes can be divided into two categories. The addition of diazo and carbene compounds to C$_{60}$, which proceeds via $[3+2]$- and $[2+1]$-cycloadditions, respectively. The other method proceeds under addition/elimination type mechanisms, for example, the Bingel cyclopropanation reaction.

1.5.1 Cycloaddition reactions to [60]fullerene

The first methano[60]fullerenes were provided by $[3+2]$-dipolar cycloaddition of diazo-compounds, e.g. 58, to [60]fullerene forming an intermediate pyrazine 59 (Scheme 1.22). Thermal or photochemical elimination of N$_2$ from 59 provided a mixture of both the methanofullerene (6,6-closed) 60 and methanoannulene (5,6-open) 61. Typically, when pyrazines of the general structure 59 are exposed to prolonged thermal conditions (toluene at reflux, 48 h) the thermodynamically favoured methanofullerene product (6,6-closed) predominates.
Chapter 1: Introduction

Scheme 1.22: Addition of diazo 58 to fullerene results in a mixture of isomers 60 and 61.

Thermal addition of other diazo-compounds such as diazomethanes,\textsuperscript{94-99} diazoacetates,\textsuperscript{94, 100} diazoamides,\textsuperscript{94} diazomethylphosphonates,\textsuperscript{101} and diazoketones,\textsuperscript{102} to [60]fullerene provides a broad variety of methano[60]fullerenes, which possess handles for further functionalisation (Schemes 1.14, 1.15 and 1.23). The methano[60]fullerene 25 can be accessed from either the \textit{tert}-butyl ester 62 (Scheme 1.23) or the \textit{O}-glycolic ester 23 (Scheme 1.15), followed by ester deprotection of the fullereny1 adducts 63 and 24, respectively. The synthetic utility of the fullereny1 carboxylic acid was demonstrated by DCC/HOBt mediated amine coupling with amino acid sequences to produce the fullereny1 peptides 64 and 26.\textsuperscript{88, 89}

Scheme 1.23: Synthesis of peptide 64 was achieved through addition of 62 to fullerene. \textit{i} – H-Thr-Thr-Asn-Tyr-Thr-OH, DCC, HOBt, C\textsubscript{6}H\textsubscript{5}Br/DMSO (6 : 1).

\[
\begin{align*}
\text{H}_2\text{C} &= \text{N}_2 & \text{C}_{60}, \text{toluene, } & 0^\circ\text{C} \text{ - RT} & \text{toluene, } \Delta \text{ or } h\nu \\
\text{58} & \rightarrow & \text{59} & \rightarrow & \text{60} \quad \text{61}
\end{align*}
\]

\[
\begin{align*}
\text{62} & \xrightarrow{\text{C}_{60}, \text{toluene, } \Delta} & 25\% & \xrightarrow{i} & \text{64} \\
63 & \text{R} = \text{tBu} & 77\% & \text{TsOH, } \Delta & 64 \text{R} = \text{H} & 31\%
\end{align*}
\]
Alternatively, a more direct route was developed to produce fullerenyl peptides by prolonged thermolysis of various diazoamides in the presence of [60]fullerene (Schemes 1.15 and 1.24).

Scheme 1.24: Thermal addition of diazoamide to fullerene provides direct access to fullerenyl amino esters.

Singlet carbenes add exclusively across 6,6-fused bonds on the [60]fullerene cage in one step. Diazirine derivatives 65 and 66 were added under thermal conditions to C_{60} via their carbene intermediates 67 to produce the isomerically pure fullerenesugar conjugates 68 and 69 (Scheme 1.25).

Scheme 1.25: Carbenes like 67 as exclusively across the 6,6-fused bond of fullerene.

Other examples of carbene [2+1]-cycloadditions to [60]fullerene include the pyrolysis of sodium trichloroacetate, and the thermolysis of oxadiazoles, cyclopropene acetalts and tosylhydrazone lithium salts in the presence of [60]fullerene.
1.5.2 Formation of methano[60]fullerenes via addition/elimination reactions

The propensity of [60]fullerene to undergo nucleophilic attack was demonstrated in Section 1.3.4. The stabilisation of the anionic intermediates (RC\(_{60}\)) to form dihydrofullerrenyl derivatives can also be achieved by intramolecular nucleophilic substitutions, if R contains a suitable leaving group. For example, the reaction of activated methylenes with [60]fullerene in the presence of a halogenating agent and base is known as the Bingel reaction and commonly yields fused 3-membered ring adducts (methanofullerenes).\(^93,107\) Addition generally occurs exclusively across the 6,6–ring junction in good yield, without the need for thermal equilibration. The Bingel reaction is one of the most widely used reactions in fullerene chemistry (Table 1.1).\(^93,107,108\)

**Table 1.1: Synthesis of methanofullerenes by addition/elimination reactions.\(^93,109,110\)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70a</td>
<td>CO(_2)Et</td>
<td>CO(_2)Et</td>
<td>Br</td>
<td>45</td>
</tr>
<tr>
<td>71</td>
<td>COCH(_3)</td>
<td>CO(_2)Me</td>
<td>Cl</td>
<td>27</td>
</tr>
<tr>
<td>72</td>
<td>COPh</td>
<td>H</td>
<td>Br</td>
<td>21</td>
</tr>
<tr>
<td>73</td>
<td>COPh</td>
<td>Ph</td>
<td>Cl</td>
<td>25</td>
</tr>
<tr>
<td>74</td>
<td>C≡CTMS</td>
<td>C≡CTMS</td>
<td>Br</td>
<td>55</td>
</tr>
<tr>
<td>75</td>
<td>Me</td>
<td>H</td>
<td>(^+)PPh(_3)</td>
<td>15-25</td>
</tr>
<tr>
<td>76</td>
<td>SPh</td>
<td>H</td>
<td>(^+)PPh(_3)</td>
<td>15-25</td>
</tr>
<tr>
<td>77</td>
<td>CO(_2)Et</td>
<td>H</td>
<td>(^\cdot)S(CH(_3))(_2)</td>
<td>58</td>
</tr>
<tr>
<td>78</td>
<td>COC(_6)H(_4)-p-OMe</td>
<td>H</td>
<td>(^\cdot)S(CH(_3))(_2)</td>
<td>42</td>
</tr>
<tr>
<td>79</td>
<td>N=CPh(_2)</td>
<td>CO(_2)CH(_2)CO(_2)Et</td>
<td>Br</td>
<td>72</td>
</tr>
</tbody>
</table>
The Bingel reaction conditions have been modified, and work in moderate to excellent yield with ketones, esters and iminoglycinates. This modification has allowed for the generation of the analogous α-haloanion in situ rather than the previous isolation of the halogenated intermediate. This efficient and reliable one-pot reaction has been used extensively with malonic esters and derivatives, as illustrated in Scheme 1.26. Alternative methods to generate methano[60]fullerene derivatives via addition/elimination mechanisms have employed sulfonium and phosphonium ylides (Table 1.1, compounds 75-78). Deprotection of the ester moieties in these methano[60]fullerenes, as well as the malonate derivatives, has provided access to versatile handles, including the carboxylic acid 25 which was generated by the addition of the sulfonium ylide 85 to C_{60}, followed by cleavage of the tert-butyl ester 63 with p-
The acid 25 was then converted to its acid chloride 86, which was subsequently treated with tributyltin azide to deliver the acyl azide 87 in good yield. Exposure of 87 to o-xylene at reflux was speculated to have afforded the isocyanate 88, which was not isolated but trapped as the tert-butyl carbamate 89. Treatment of 89 with TfOH provided the amine salt 90, which was coupled to various acyl chlorides (91) to generate the corresponding amide derivatives 92.119

Scheme 1.27: Synthesis of amides 92 was achieved through a Curtius rearrangement.

The only true α-fullereryl amino acid synthesized thus far is fulleroproline (Fpr, 93); albeit a fullerene-fused proline derivative.69 The synthesis of acyclic α-fullereryl
amino acids such as α-[60]fullerenyglycine (Fgly, 94) or related derivative 95, akin to
the majority of natural amino acids had remained elusive (Scheme 1.28).

![Scheme 1.28: The only true α-fullerenyglycine acid synthesised thus far is Fpr.](image)

Previous work in our laboratory reported that the addition of \( N \)-
diphenylmethyleneglycinate esters (96) to [60]fullerene under Bingel
cyclopropanation reaction conditions provided the methano[60]fullerene derivatives 97
(Scheme 1.29).\(^{109,110}\)

![Scheme 1.29: Addition of iminoglycinates to fullerene under Bingel cyclopropanation
conditions provided methanofullerenes 97.](image)

The deprotection of both the amine and the carboxylic acid proved difficult. The
hydrolysis of the tert-butyl and ethyl ester analogous of 97 was attempted under both
strong and weak acid conditions, as well as basic conditions.\(^{109}\) Similarly,
diphenylimines are normally hydrolysed under mild acid conditions to the
corresponding amines,\textsuperscript{120} and despite numerous attempts to hydrolyse the imine moiety of 97 with a variety of different acids, only starting material remained.\textsuperscript{108, 109}

Activation of 97 with boron trifluoride-diethyl etherate then reduction with sodium cyanoborohydride delivered not the expected reduced imine derivative 98 but rather the ring-opened derivative 99 (Scheme 1.30).\textsuperscript{110} The ring-opened products 99 are protected versions of Fgly, 94, however all attempts to deprotect these compounds, either at the amino (via hydrogenolysis) or the ester (via acid hydrolysis) functionalities, were unfruitful.\textsuperscript{108-110}

\begin{itemize}
  \item 98
  \item 97a-c
  \item 99a-c
\end{itemize}

\begin{align*}
\text{BF}_3 \cdot \text{Et}_2 \text{O}, \text{NaCNBH}_3 \\
\text{CH}_2\text{Cl}_2/\text{MeCN} \\
44-58\%
\end{align*}

\textbf{Scheme 1.30}: Compound 97 could not be reduced to 98, but rather was reduced to the protected fullerenyl glycinate 99.

\section*{1.6 Regioselective addition of multiple addends to [60]fullerene}

The concept of using the [60]fullerene cage as a three-dimensional template in medicinal chemistry, nanotechnology and materials science is well established. For this to be fully realised the production of chemical handles or synthons in precisely defined positions around the carbon spheroid is required. A wide range of synthetic protocols for the synthesis of mono-substituted [60]fullerenyl derivatives already exist. In contrast, the sequential addition of addends to C\textsubscript{60} has been problematic with many regioisomers being obtained, requiring tedious chromatographic separations.\textsuperscript{121-123} For
example, the addition of 1 molar equiv. of the bromomalonate 100 to methano[60]fullerene 70 under Bingel cyclopropanation reaction conditions produced a complex mixture of 8 regioisomers (Scheme 1.31, see Section 4.2.1 for details).

**Scheme 1.31:** Addition of independent addends to fullerene almost always results in a complex mixture of isomers.

One way to overcome the lack of selectivity experienced with the addition of independent addends to C$_{60}$ is through the use of a tether, which attaches reactive groups together through a typically rigid linker molecule (Scheme 1.32). This concept was developed by Diederich and coworkers,$^{124}$ and has allowed for the formation of all possible bis-addition patterns to [60]fullerene.$^{9,125,126}$

**Scheme 1.32:** Tether-mediated addition of addends limits the number of regioisomers.

Much work has been done trying to determine the influences on regiochemical outcome, with the precise details still uncertain.$^{126,127}$ The tether length and mechanism of addition to the carbon spheroid play a role, but surprisingly other factors such as the nature of the leaving group at tethered active moieties, also impact on regiochemical outcomes.$^{127}$ Hence, predicting the regiochemical outcome of such reactions is often
difficult. To illustrate this point, the tethered bismalonate derivatives from \textit{meta} benzenedimethanol, produced the \textit{cis}-2 bisadduct 101 under Bingel cyclopropanation reaction conditions (Scheme 1.33).\cite{113} Using the same benzenedimethanol tether and reaction conditions with diphenyliminoglycinate reactive groups the regiochemical outcome was different (Scheme 1.33). This reaction is further discussed in Section 4.3.

\textbf{Scheme 1.33:} Addition of same tether but with different reactive groups to fullerene under Bingel cyclopropanation conditions provided different regioisomers.

\section{1.7 Project Aims}

The initial aim of this project was the synthesis and Bingel cyclopropanation reaction of imine-protected amino esters to [60]fullerene (Scheme 1.34). Selective deprotection of the resultant methano[60]fullerene amino and carboxyl ends followed by coupling to amino acids would provide novel fullereryl peptides, of the general structure 102 and 103. The conformations of these structures could then be determined using various 2D-NMR techniques. Alternatively the methano[60]fullerene could be ring-opened and then deprotected and coupled to amino acids (Scheme 1.34).
Scheme 1.34: Synthetic plan to access fullerenyl peptides of the general structure 102.

These studies would then be further extended to the synthesis of protected bicyclopropyl fullerenyl amino acids using tethered bis-α-iminoglycinates under Bingel cyclopropanation reaction conditions (Scheme 1.35). The precise structures of these adducts would be determined using well-established 2D-NMR techniques. Selective deprotection of these structures would provide bisadducts analogous to 94 and 95 that could potentially be coupled to different peptides forming fullerenyl peptides of the general structure 104 and 105. The two protons on the fullerene cage of the bisring-opened compound 105 would also provide a starting point for long-range $^1$H to $^{13}$C correlations to be observed by NMR experiments, opening the possibility of “walking” from one non-equivalent fullerenyl proton to the other, thereby determining the regiochemical outcomes.
Scheme 1.35: Synthetic plan to access fullerenyl bis-peptides of the general structure 105.
2.1 Structural reassignment of the addition products of diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation conditions

The addition of diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation reaction conditions was originally reported to furnish the corresponding methano[60]fullerene derivatives 97a-b (Scheme 2.1).\textsuperscript{109, 110} The key to the structural elucidation of 97a-b was the observation of a single sp\textsuperscript{3} carbon fullereneyl resonance (between 82-83 ppm) in the \textsuperscript{13}C NMR spectrum when CDCl\textsubscript{3}/CS\textsubscript{2} was used as solvent. This implied that a symmetry plane bisected the substitution site, and hence supported the structural assignment of a methano[60]fullerene. However, as a part of this study we re-examined the \textsuperscript{13}C NMR spectra of these compounds at higher NMR field (150 MHz). This revealed that this resonance was actually split into two sp\textsuperscript{3} fullerene resonances separated by 0.02-0.03 ppm. Further downfield, 28 full-intensity and 2 half-intensity fullereneyl carbon sp\textsuperscript{2} resonances were present thus indicating the existence of a plane of symmetry. The equivalence of the aromatic rings was shown in the \textsuperscript{1}H NMR spectrum, which indicated that this symmetry plane bisected these two rings. Together this information indicated that the fullereneyl sp\textsuperscript{3} carbons must also lie on the plane of symmetry, thereby ruling out the possibility of a cyclopropyl ring (methano[60]fullerene).

\textbf{Scheme 2.1:} The addition of diphenyliminoglycinates to fullerene under Bingel cyclopropanation conditions was originally reported to furnish methanofullerenes 97.\textsuperscript{109, 110}
Examination of the long-range $^1$H to $^{13}$C NMR correlations provided evidence for the alternative structures 106a-b rather than 97a-b (Figure 2.1), with a strong HMBC correlation existing between the ortho-protons of the phenyl rings ($H_\alpha$) (Figure 2.1) and the dihydropyrrole sp$^3$ carbon resonance ($C_\beta$) at 95.9 ppm (Table 2.1). Such a correlation would have been expected for 106a-b but not 97a-b (Figure 2.1). Furthermore, no correlations were observed to any downfield resonance that could be attributable to an imine carbon (e.g. the resonance at 159.7 ppm). Thus the product outcomes from the addition of diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation reaction conditions is not the previously reported methanofullerenes 97a-b but rather the diphenyldihydrophylldihydropyrrole 106a-b.$^{128}$

![Potential structural outcomes from the addition of various diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation reaction conditions](image)

**Figure 2.1:** Potential structural outcomes from the addition of various diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation reaction conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>$H_\alpha$ (ppm)</th>
<th>$C_\beta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>106a, R = Et</td>
<td>8.10</td>
<td>95.9</td>
</tr>
<tr>
<td>106b, R = 'Bu</td>
<td>8.05</td>
<td>96.0</td>
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</table>

A proposed mechanism (not necessarily concerted) for the formation of the fullerenyldihydropyrroles 106 is shown in Scheme 2.2. Ring-closure of the anionic
intermediate A, would favour formation of the five-membered (dihydropyrrole) ring 106 over the more strained three-membered (cyclopropane) ring 97.

Scheme 2.2: The addition of iminoglycinate to fullerene under Bingel cyclopropanation conditions provides the analogous fullerényldihydropyrrole 106, with proposed mechanism shown with blue arrows, and not the previously reported methanofullerene 97, shown with red arrows.

2.1.1 A 2D-INADEQUATE study of diphenylfullerenyldihydropyrrole 106a

Prior to this study, a 2D-INADEQUATE spectrum of a $^{13}$C enriched (10%) sample of 106a was collected to examine carbon-carbon connectivities. However the spectrum was not successfully analysed based on the assumed structure 97a. Re-examination of the original spectrum was therefore conducted, as a part of this study, in an attempt to assign all the carbon atoms in the fullerene cage.

Fullerenyl resonances were distinguished from non-fullerenyl resonances by the presence of $^{13}$C-$^{13}$C coupled satellites situated on either side of a central resonance peak. Thus, the resonance located at 140.8 ppm was assigned as the ipso carbons corresponding to the diphenyl moiety (Figure 2.2). Assignment of the carbon sphere
was achieved on the basis of one-bonded $^{13}$C-$^{13}$C connectivities and examination of the carbon-carbon coupling ($^{1}J_{CC}$) values knowing typical values for C(sp$^{2}$)-C(sp$^{3}$) bonds (~48 Hz), the longer 5,6 ring-fused bonds (54-57 Hz) and the shorter 6,6 ring-fused bonds (65-71 Hz).$^{31, 108, 109, 128-130}$

Resonances of the diphenyl ipso carbons

**Figure 2.2:** $^{13}$C NMR spectrum (150 MHz, CDCl$_3$/CS$_2$; 6/4) of 106a. The top spectrum is of the natural abundance sample and the bottom spectrum is of the 10% $^{13}$C enriched sample.

The full 2D INADEQUATE spectrum of 106a is shown in Figure 2.3. The two expected half-intensity fullerenyl sp$^2$ resonances, which arise from carbon atom(s), which lie on the plane of symmetry, are clearly resolved and appear at 146.8 and 146.9 ppm, for C52 and C60 respectively, and represent the starting point for the analysis of the carbon-carbon connectivites (Figures 2.3a and 2.3b). Typically, the starting point for analysis is the fullerene sp$^3$ region, however it was not included in the INADEQUATE spectral window as the additional cost in terms of acquisition time was not considered worthwhile.
Figure 2.3: a) Expansion of the 2D INADEQUATE spectrum (150 MHz, CDCl₃/CS₂; 3 : 2) of 106a. The starting point for analysis was the half-intensity peak for C52. The half-intensity peaks (C52 and C60) arise from the carbon atoms lying within a plane of symmetry. b) 2D INADEQUATE full spectrum (150 MHz, CDCl₃/CS₂; 3 : 2) of 106a.
Starting at C52 (Figure 2.3a, Table 2.2), a correlation to C53/51 (145.5 ppm) was observed with a relatively small coupling constant ($J_{C-C}$ = 56.4 Hz), typical for 5,6 ring fusion carbons. Carbons 51/53 showed a correlation to C35/36 ($J_{C-C}$ = 56.3 Hz), and to C50/54, however a $J_{C-C}$ value could not be accurately determined due to peak overlap. From C35/36 a correlation to C34/37 was observed, which showed two correlations, as opposed to three. This occurs when a resonance lies on or adjacent to the plane of symmetry, since this was a full-intensity peak it must be the later. Following the plane of symmetry will lead to the fullerene substitution (sp$^3$) site. To this end, C34/37 was found to correlate to both C33/38 ($J_{C-C}$ = 55.9 Hz) and C16/17 ($J_{C-C}$ = 55.8 Hz). C16/17 correlated to only one full-intensity resonance C15/18 ($J_{C-C}$ = 56.4 Hz) again indicating that this carbon atom was located directly adjacent to the symmetry plane. From C15/18 correlations to C14/19 ($J_{C-C}$ = 56.4 Hz) and to C3/4, which had a larger coupling constant ($J_{C-C}$ = 67.6 Hz), typical for 6,6 ring fusion carbons were observed. From C3/4 a correlation to C2/5 ($J_{C-C}$ = 57.1 Hz) was noted. From C2/5 a large $J_{C-C}$ coupling constant (72.4 Hz) to C12/6 was present, indicative of a 6,6-ring fusion whilst a coupling from C2/5 to C1 ($J_{C-C}$ = 43.4 Hz) was observed, with the magnitude of this coupling constant indicative of C(sp$^2$)-C(sp$^3$) connectivity. This process was continued and the entire carbon cage was assigned, as shown in Figure 2.4 and Table 2.3.
Figure 2.4: Schlegel diagram of 106a, with the red lines and numbers signifying the correlations discussed in text and shown in Figure 2.3a/b. The ester and phenyl groups were omitted for clarity.
### Table 2.2

Chemical shifts (δ), peak assignments, and carbon-carbon coupling constants ($^1J_{CC}$) for the [60]fullerene cage of 106a (150 MHz, CDCl$_3$:CS$_2$, 3:2).

<table>
<thead>
<tr>
<th>Carbon Number</th>
<th>δ (ppm)</th>
<th>(Correlated Carbon) $^1J_{C-C}$/Hz</th>
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<tr>
<td>1$^{ac}$</td>
<td>82.71</td>
<td>(2) 43.4</td>
</tr>
<tr>
<td>2,5</td>
<td>153.06</td>
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<td>145.02</td>
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<tr>
<td>6,12</td>
<td>134.55</td>
<td>(2) 72.4, (11) 54.2, (13) 57.3</td>
</tr>
<tr>
<td>7,11</td>
<td>136.53</td>
<td>(12) 54.2, (10) 71.3, (29) 57.2</td>
</tr>
<tr>
<td>8,10</td>
<td>148.49</td>
<td>(11) 71.3, (9) 41.5, (26) 57.5</td>
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<tr>
<td>9$^{ac}$</td>
<td>82.71</td>
<td>(10) 41.5</td>
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<td>13,20</td>
<td>141.71</td>
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<td>16,17</td>
<td>141.69</td>
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<td>60$^{a}$</td>
<td>146.93</td>
<td>(59) 55.9</td>
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</table>

$^{a}$Denotes half-intensity peaks, $^{b}$denotes peak overlap, $^{c}$unable to differentiate, $^{d}$1$J_{C-C}$ values could not be accurately measured.

### 2.2 Reductive ring-opening reactions

The structures of the reductive ring-opened products of compounds 106a-b, the 1,9-dihydro[60]fullerenylglycinates 99a-b, with sodium cyanoborohydride are correct as previously published (Scheme 2.3). However, in light of these recent structural
revisions the speculated reaction mechanism required adjustment. Therefore, upon addition of the Lewis acid to form 107, the now proposed intermediate 108 (Scheme 2.3) undergoes ring-opening to give the more stable conjugated diphenylmethylenimine fullerenyl anion intermediate 109A, rather than the less conjugated imine, the fullerenyl anion intermediate 109B. Furthermore the ester group in 109B may destabilise the iminium ion moiety due to its electron withdrawing nature. Further reduction of the imine moiety of 109A followed by protonation provides the 1,9-dihydro[60]fullerenylglycinates 99a-b.  

\[
\begin{align*}
\text{106a-b} & \xrightarrow{\text{BF}_3\text{Et}_2\text{O}} \text{NaCNBH}_3 \\
\text{106a-b} & \xrightarrow{\text{BF}_3\text{Et}_2\text{O}} \text{NaCNBH}_3 \\
\text{107} & \xrightarrow{\text{NaCNBH}_3} \text{108} \\
\text{108} & \xrightarrow{\text{NaCNBH}_3} \text{109A} \\
\text{109B} & \xrightarrow{\text{NaCNBH}_3} \text{109B} \\
\text{109A} & \xrightarrow{\text{H}^+} \text{99a; } R = \text{Et} \\
\text{109B} & \xrightarrow{\text{H}^+} \text{99b; } R = \text{`Bu} \\
\end{align*}
\]

Scheme 2.3: The proposed mechanism for the reductive ring-opening of fullerényldihydropyrroles 106 to provide their analogous dihydrofullerenyl derivatives 99.

2.2.1 Optimisation of the reductive ring-opening reaction conditions

The reductive ring-opening reaction conditions previously established in our laboratory are sufficient for simple [60]fullerenylidihydropyrroles 99 however
optimisation would allow for use in more complicated systems (e.g. bis-adducts). Hence a comprehensive study was conducted, as part of this thesis, to optimise the conditions for reductive ring-opening of 106a before using this methodology on structurally more complex compounds (Table 2.3).

Under the previously published reductive ring-opening conditions (entry 1, Table 2.3), 109, 110 99a was isolated in 48% yield along with a significant quantity of pristine fullerene (40%). The later was expected to arise from collapse of the anionic intermediate 109A (Scheme 2.4) to form C_{60} and the reduced addend 110. As a modification of the published procedure glacial acetic acid was used to quench the proposed anionic intermediate in situ. This resulted in a slight increase in the yield of 99a, supporting our proposed mechanism (entries 8-12, Table 2.3). Intriguingly, a minimum of 6 molar equivalents of the reducing agent (NaCNBH₃) was required to affect ring-opening with 10 molar equivalents being optimal (entries 3, 10-12). Strict control of the stoichiometry of the Lewis acid (BF₃.OEt₂) was found to be critical to maximising the yield; too much led to significant degradation to pristine fullerene (entries 4 and 7). Conversely, without the Lewis acid activation of the imine, ring-opening did not occur (not shown in Table 2.3). The use of a weaker Lewis acid (titanium tetraisopropoxide) was trialled in an attempt to activate the imino-nitrogen (see Scheme 2.3) without promoting degradation to C_{60} (entries 13 and 14). Unfortunately, even with 20 molar equiv. of this Lewis acid and longer reaction times (16 h), only traces of the ring-opened compound 99a was generated as indicated by TLC analysis, which showed mainly unreacted starting materials.
Scheme 2.4: Anionic intermediate 109A can proceed in two different directions. In the absence of a proton source 109A extruded the reduced addend 110 to form [60]fullerene. Through the addition of a proton source (acetic acid) an increased yield of the ring-opened product 99a has been observed.

Increasing the concentration of the starting material led to a decrease in the yield of 99a and an increase in pristine fullerene (entries 2 and 5), hence relatively low concentrations of 106a (0.5-1 mg/mL) favourably influenced the reaction outcome (entry 17). It is possible that even lower reaction concentrations of 106a could result in better conversion to 99a, but this was viewed as impractical for the early stages of a potentially long sequential synthesis. The relative amount of co-solvent (THF or MeCN) also played a key role in solubilising the reducing agent (entries 2, 6, 8 and 18). The best results were found when THF or MeCN was added in a 1 : 2 ratio (v/v) with CH₂Cl₂. Increasing the ratio past this point lead to precipitation of the starting material. Also, a shorter reaction time (45 min) and lower temperature (0 °C) resulted in an increase in yield of 99a and a decreased yield of fullerene.

In summary, the best conditions found (entry 17) involved the addition of glacial acetic acid (1.8 mmol) to a 0.5 mg/mL solution of 106a at 0 °C, which was stirred for 45 min leading to an increased yield of 99a from 48% to 68% and a decrease in C₆₀ formation from 40% to 13%.
## Table 2.3: Optimisation of reductive ring-opening of 106a to 99a

<table>
<thead>
<tr>
<th>Entry</th>
<th>[106a] mg/mL</th>
<th>NaCNBH₃ (equivs.)</th>
<th>BF₃(OEt)₂ (equivs.)</th>
<th>Ti(OiPr)₄ (equivs.)</th>
<th>AcOH (mmol)</th>
<th>Temp (°C)</th>
<th>CH₂Cl₂/THF (%)</th>
<th>99a (%)</th>
<th>C₆₀ (%)</th>
<th>Time (min)</th>
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<td>61</td>
<td>13</td>
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*Required 5/1 CH₂Cl₂/THF for solubility, equiv.= molar equivalents, RT = room temperature
2.3 From fullerenyldihydropyrrole derivatives towards fullerenyld peptides

With the goal to synthesise fullerenyld peptides, a retrosynthetic analysis for the synthesis of a peptide containing $\alpha$-fullerenylglycinate within an amino acid sequence was made (Scheme 2.5). Starting with the known fullerenyldihydropyrrole 106 it could be possible to access the fullerenyld peptide 110 via two different but related synthetic paths.

Scheme 2.5: Retrosynthetic analysis for the synthesis of fullerenyld peptides 110 from the known diphenylfullerenyldihydropyrroles, was attempted using two different but related pathways.
In a forward synthetic sense, Path A starts with the known diphenylfullerenyl dihdropyrroles 106 and proceeds through the established transformation to the protected fullerenylglycinate 99. It was anticipated that removal of the benzhydryl group would provide access to the key intermediate amino ester 111, which could subsequently be coupled to N-protected amino acids of choice using well established peptide coupling chemistry. Subsequent deprotection of the carboxyl end followed by coupling with another peptide could potentially provide a general method for the synthesis of peptides containing \( \alpha \)-substituted fullerenyl amino acids.

Alternatively, access to fullerenyl peptides could be achieved via Path B. Starting with the known fullerenyl compounds 106 deprotection of the carboxyl group provides the carboxylic acid 114, which should readily couple to amino esters under standard coupling conditions to afford dihdropyrrole peptides of the general structure 115. Subsequent ring-opening should provide the dihydro derivative 116, which upon removal of the benzhydryl group, gives access to the free amine allowing for peptide coupling with amino esters to furnish \( \alpha \)-substituted fullerenyl peptides.

### 2.3.1 Ethyl [60]fullerenylglycinate (Path A)

The first step in Path A was the reductive ring-opening reaction of 106a (Section 2.2) using the established optimised conditions. Reductive removal of the benzhydryl group of racemic 99a was achieved by treatment of 99a in TFA/CH\(_2\)Cl\(_2\) with triethylsilane at 45 °C for 30 min providing the novel, key intermediate, ethyl \( \alpha \)-[60]fullerenyl glycinate 111a. This represents the first known “free” N-terminal acyclic \( \alpha \)-[60]fullerenyl amino ester (Scheme 2.6). This compound could be purified by column chromatography, using CH\(_2\)Cl\(_2\) as the eluent. However, attempts to isolate the free amine 111a, by removal of the solvent,
resulted in material that was difficult to re-dissolve making structural analysis via spectroscopic techniques (e.g. NMR) difficult. However, 111a was sufficiently soluble to acquire an ESI mass spectrum which displayed a peak at m/z 824, assigned as the molecular ion (M+H)^+. Hence, for all chemistry involving compound 111a, the column chromatography fractions containing this compound were pooled together, washed with mild aqueous base, dried and then used immediately as a solution in subsequent derivatisation reactions.

**Scheme 2.6:** Synthesis of ethyl α-fullerenylglycinate 111a, was achieved by the reductive removal of the benzhydryl moiety of 99a. The amine 111a was trapped as the more stable acetamide derivative 118.

In order to prove the formation of the free amine 111a, a freshly prepared solution of 111a in CH$_2$Cl$_2$ was treated at RT with acetic anhydride for 6 h. Purification of the crude mixture by column chromatography afforded the more soluble N-acetamido derivative 118 in 47% overall yield from 99a (Scheme 2.6). The structure of 118 was clearly evident from analysis of the $^1$H NMR spectrum, which showed a 1H singlet at 6.92 ppm, indicating retention of the fullerenyl proton (H$_a$, Scheme 2.6), while a singlet at 2.39 ppm, with a relative integration of 3H, was assigned to the acetyl methyl protons. Analysis of the $^{13}$C NMR spectrum of 118 indicated no plane of symmetry with 52 fullerenyl sp$^2$ carbon resonances present, six of which were double-intensity peaks which occur when two carbon
resonances coincidentally overlap in the $^{13}$C NMR spectrum giving rise to a peak with twice the relative intensity. Examination of the HSQC spectrum indicated the proton assigned as the fullerenyl proton was attached to a carbon at 57.8 ppm, characteristic of a dihydrofullerenyl $sp^3$ resonance. Analysis of the HMBC spectrum detailed a strong correlation from the fullerenyl proton $H_a$ to an upfield resonance at 67.9 ppm assigned as the quaternary fullerenyl $sp^3$ resonance. A large number of additional correlations to the fullerene $sp^2$ carbons were also observed from this proton. The resonance at 6.63 ppm in the $^1H$ NMR spectrum, assigned as the methine proton ($H_b$) of the glycinate moiety, showed a correlation in the HMBC spectrum to the quaternary fullerenyl $sp^3$ resonance (67.9 ppm), along with a strong correlation to a downfield resonance at 170.1 ppm assigned as the ester carbonyl, thus confirming the proposed connectivities. Confirmation of the structure was provided by ESI-MS, with the spectrum showing a peak at $m/z$ 866, which was assigned as the molecular ion (M+H)$^+$.  

2.3.2 Intramolecular Mannich reaction with ethyl fullerenylglycinate.  

Additional proof for the formation of the amine 111a would be the successful preparation of an imine derivative. To this end, a solution of the amine 111a was treated with cyclohexanone (~2 equivs.) at RT for 10 h, with the aim of trapping 111a as its imine derivative. The crude mixture was then reduced in volume and directly applied to a silica gel column to provide the unexpected spirocyclic fulleropyrrolidine 119 in 42% yield over two steps (Scheme 2.7). Analysis of the $^1H$ NMR spectrum of 119 revealed a downfield singlet at 5.63 ppm with a relative integration of 1H, indicative of the $\alpha$-proton to the ester on the pyrrolidine ring. The splitting pattern of the resonances at 4.29 and 4.43 ppm, assigned as the $CH_2$ of the ethyl ester, indicated its close proximity to a stereogenic atom.
Analysis of the $^{13}$C NMR spectrum of 119 indicated addition of the cyclohexyl ring with five methylene resonances at 23.2, 24.2, 26.2, 37.0 and 38.3 ppm and a quaternary spiro carbon resonance at 74.4 ppm. The fullerenyl sp$^2$ chemical shift region displayed 58 resonances indicating the absence of symmetry. Additionally, long-range $^1$H to $^{13}$C correlations from the protons adjacent (both axial and equatorial) to the spirocyclic atom to the fullerenyl sp$^3$ carbons confirmed the connectivity from the cyclohexyl ring to the fullerene cage. The pyrrolidine methine proton (5.63 ppm) also showed correlations to both the sp$^3$ and some sp$^2$ fullerenyl carbons and cyclohexyl resonances confirming the assigned five-membered ring structure. The ESI mass spectrum showed a peak at $m/z$ 904, which was assigned as the molecular ion (M+H)$^+$. The unexpected product 119 most likely arises via a Mannich type reaction.

Scheme 2.7: The amine 111a was found to readily undergo an intramolecular Mannich reaction with cyclohexanone, acetone and pivaldehyde to furnish the corresponding fulleropyrrolidines 119-120.

The participation of fullerenyl derivatives in Mannich reactions has not been previously reported. Unlike the more traditional methods for the synthesis of
fulleropyrrolidines$^{90, 92}$ which require heating, this reaction represents a new and mild method for their synthesis, at RT and without the addition of base. The proposed mechanism for the formation of 119 occurs via nucleophilic attack of the amine onto the carbonyl group of the cyclohexanone (Scheme 2.8) forming the intermediate A; the oxy-anion intermediate then abstracts a proton from the amino cation forming the neutral intermediate B. This intermediate then undergoes dehydration forming intermediate C, and water, with an equilibrium existing between the intermediates C and D arising from intramolecular hydrogen transfer. In intermediate D, a reactive iminium cation, can be attacked by the fullerenyl anion in an irreversible step forming the corresponding fulleropyrroolidine. It has been estimated that the pK$_a$ of dihydrofullerene is approximately 4.7,$^{131}$ therefore proton transfer in these systems would be feasible.

![Scheme 2.8](image)

**Scheme 2.8:** Ethyl fullerenylglycinate has been found to readily participate in an intramolecular Mannich reaction with some simple ketones and pivaldehyde.

To further examine the scope of this reaction, acetone was added to a solution of the amine 111a under analogous conditions, providing the dimethylpyrrolidine 120 in 48%
yield (over two steps, Scheme 2.7). This compound has previously been synthesised albeit by a different method, and was only characterised by $^1$H NMR, FTIR and FDMS. Analysis of the $^{13}$C NMR spectrum of the sample synthesised here showed the fullerényl sp$^2$ chemical shift region containing 53 of the expected 58 resonances. Upfield the two fullerényl sp$^3$ resonances were clearly visible at 76.5 and 78.2 ppm, which is a characteristic chemical shift for such carbons. The non-equivalence of the methyl groups on the pyrrolidine ring was demonstrated by two resonances at 28.2 and 29.4 ppm assigned as the trans and cis methyl groups, relative to the ester, not necessarily respectively. Further confirmation of the structure of 120 was provided by analysis of the ESI mass spectrum with the peak at $m/z$ 864 assigned as the molecular ion (M+H)$^+$. Further extension of this type of reaction with pivaldehyde provided the analogous pyrrolidine 121 in 16% yield and as a 8 : 5 mixture of the cis and trans isomers. Attempts to condense 111a with benzaldehyde or (-)menthone, which was accessed via a Swern oxidation of (-)menthol, were unsuccessful with the return of starting material after 24 h. It may have been possible to obtain the desired fulleropyrrolidines through Lewis acid activation of the carbonyl group of the starting material, however this was not attempted.

To conclude, this small study shows that the intramolecular Mannich reaction described above is not currently a general method for access to fulleropyrrolidines, but rather a method for the generation of simple ketone and pivaldehyde derived fulleropyrrolidines. However, further development may provide a general reaction applicable to a wider range of carbonyl compounds.
2.3.3 Amine coupling of ethyl fullerenylglycinate (111a) with amino acids

With the structure of the ethyl α-[60]fullerenyl glycinate 111a established, the coupling of this amine with N-Boc-glycine was attempted. Thus a solution of the amine 111a was treated with N-Boc-glycine (1.2 equivs.), which had been activated for coupling with EDCI/HOBt. Unfortunately, none of the desired amine coupled product was isolated, with a quantitative return of starting material. This was speculated to be due to the steric hinderance caused by the relatively close proximity of the amino group to the fullerene cage. The electron withdrawing effect of the fullerene cage was thought to be less of an issue as the amine 111a was readily acetylated and also participated in Mannich type reactions (Sections 2.3.1 and 2.3.2). Since the amine 111a was acetylated using acetic anhydride it was thought promising to generate the analogous N-Boc-glycine anhydride and attempt addition to the amine 111a. Access to the anhydride was achieved using DCC and N-Boc-glycine in a known procedure. Disappointingly, the instability of the anhydride lead to decomposition before significant addition to the fullereryl amino group could occur. Since acid chlorides are slightly more reactive and offer less steric demand than their analogous anhydrides, they were examined next. The amine of glycine was protected with a phthyl group and the acid chloride 122 was generated using thionyl chloride in quantitative yield (Scheme 2.9). The crude acid chloride was then added to a suspension of the fullereryl amine 111a and solid NaHCO₃ in CH₂Cl₂. The reaction was stirred at RT for 16 h and then the crude mixture was concentrated in vacuo and subjected to silica gel chromatography. Elution with CH₂Cl₂/hexanes (7 : 3) provided the racemic acyclic α-substituted fullereryl peptide 123 in 29% yield, over the two steps (Scheme 2.9).
Chapter 2: Synthesis of Fullerenyl Peptides

Scheme 2.9: N-Alkylation of the fullerenyl amine 111a with acid chloride 122 afforded α-fullerenyl peptide 123.

Analysis of the $^1$H NMR spectrum of 123 indicated successful coupling with the appearance of a broad doublet at 7.77 ppm with a relative integration of 1H assigned as the amide proton. Additionally, a strong singlet at 6.86 ppm indicated retention of the fullerenyl proton. The characteristic pair of doublet of doublets at 7.72 and 7.88 ppm, with a relative integration of 2H each, signified the presence of the phthyl protecting group. Due to the presence of the stereogenic centre in 123, it was expected that the phthalglycyl methylene protons would be diastereotopic (AB system) however a coincidental overlap was observed. The addition of d$_6$-benzene (50 µL) to the deuterated chloroform solution provided sufficient signal shift and allowed for observation of the expected AB quartet for these protons. Further evidence for the structure of 123 came from the analysis of its $^{13}$C NMR spectrum with 51 of the 58 expected fullerenyl sp$^2$ (7 overlapping resonances) and the 2 sp$^3$ resonances being observed. The sp$^3$ chemical shifts (57.5 and 67.8 ppm) were consistent with a dihydrofullerenyl structure.$^{109, 110}$ Long-range $^1$H to $^{13}$C correlations showed a 4-bond coupling from the phthalglycyl methylene protons to H$_B$ at 6.58 ppm,
while a 3-bond correlation from $H_\beta$ to $C_\alpha$ confirmed the 1,9-substitution pattern on the fullerene cage (Figure 2.5). Confirmation of the structure was provided by analysis of the mass spectrum with a peak at $m/z = 1033$ observed and assigned as the sodiated molecular ion $(M+Na)^+$. 

**Figure 2.5**: HMBC (600 MHz, CDCl$_3$) spectrum of the fullereryl peptide 123 detailing the 3-bond $^1$H to $^{13}$C connectivities from the fullereryl proton ($H_\alpha$) to methine carbon ($C_\beta$).

The relative acidity of the fullereryl hydrogens is well documented,$^{109, 110, 131}$ and therefore restricted the use of strong base in these amide coupling reactions. However, it was found that the use of NaHCO$_3$ does not cause deprotonation of the starting material and
is thus able to be used to neutralise the HCl by-product, which would otherwise deactivate
the fullerenyl amine by forming the analogous hydrochloride salt.

2.3.4 Extending amine coupling to peptides

In order to explore the versatility of the coupling reaction between the amine 111a
and acid chlorides, phthylGlyglycinoyl chloride 124 was synthesised (Scheme 2.10). The
precursor for acid chloride synthesis was accessed from the condensation of Gly-Gly with
phthalic anhydride. The poor solubility of the dipeptide proved problematic for the amine
protection. Therefore the reaction was performed without solvent using five molar
equivalents of the anhydride at 200 °C. After 1 h, the reaction mixture was cooled, then
washed sequentially with CH₂Cl₂ and methanol to remove the excess anhydride and
unreacted GlyGly respectively, providing phthylGlyGly 125 in 74% yield as a white
solid.¹³⁵ Since this compound was first synthesised prior to modern characterisation
techniques (e.g. NMR) only its melting point was reported. To the best of our knowledge
the NMR has not been reported in the literature. Therefore, analysis of the ¹H NMR
spectrum of 125 indicated coupling through the relative integration of the phthyl protons
being double that of the two singlets at 4.42 and 3.93 ppm, which were assigned as the
methylene protons. Examination of the ¹³C NMR spectrum of 125 indicated the presence of
the phthyl group along with two upfield resonances at 41.9 and 40.8 ppm assigned as the
methylene carbons. Confirmation of the structure was provided by inspection of the ESI-
MS spectrum with a peak at m/z 263 assigned as the molecular ion.
Conversion of the peptide 125 to the corresponding acid chloride 124 was unsuccessful utilising the same procedure for the analogous conversion of phthylglycine. It appeared that the conditions were too harsh with a suspension of 125 in freshly distilled thionyl chloride and toluene turning into a dark black solution in minutes. Analysis of the \(^1\)H NMR spectrum of the crude mixture indicated complete degradation to an unknown mixture. One possible side reaction is the acid chloride intermediate 124 undergoing intramolecular cyclisation through the amide carbonyl group under the high temperature reaction conditions.

To gain access to the acid chloride 124, oxalyl chloride and a phase transfer catalyst were added to the N-protected dipeptide 125 which was stirred at RT for 1 h. Removal of the solvent provided the crude acid chloride 124, which was used in subsequent reactions without further purification. The acid chloride was extremely sensitive and to prove its identity it was converted to the known methyl ester 126 in 93% yield by nucleophilic substitution with methanol in pyridine (Scheme 2.10).\(^{136}\)
Chapter 2: Synthesis of Fullerenyl Peptides

Having established the protocol to generate the acid chloride 124, the coupling to the fullerenyl amino group in 111a was attempted (Scheme 2.10). The CH₂Cl₂ solution containing the amine 111a was treated with powdered molecular sieves and stirred for 15 min before the addition of solid NaHCO₃ and the acid chloride 124. Analysis of the reaction mixture by TLC indicated that after 6 h the acid chloride had been totally consumed, however the amine 111a remained unchanged. It was speculated that the acid chloride was too unstable.

2.3.5 Fmoc amino acid chlorides

The important discovery of the enhanced stability associated with Fmoc amino acid chlorides by Carpino has dramatically altered the use of acid chlorides in peptide synthesis.¹³⁷ This method provided promise to overcome the stability issues encountered with both the phthyl acid chloride 124 and N-Bocglycine anhydride derivatives. Hence in a modified literature procedure,¹³⁸ a suspension of Nα−Fmoc-Nε-Boc-L-Lysine (127) and solid Na₂CO₃ in CH₂Cl₂ was treated with thionyl chloride and sonicated for 30 min, to deliver the corresponding crude acid chloride 128, which was used immediately in the subsequent reaction (Scheme 2.11). Therefore, a suspension of the amine 111a in CH₂Cl₂ and solid NaHCO₃ was treated with the crude acid chloride 128 and the reaction mixture stirred for 16 h at RT to provide the fullerenyl peptide 129 as an inseparable 1 : 1 mixture of diastereomers. Unfortunately, the unreacted (excess) acid chloride 128 converted to the acid 127 upon work-up, and possessed a similar retention time on silica gel as the dipeptide 129. Washing with methanol removed most of 127, however absolute purity was not achieved for this preliminary investigation.
Proof of the structure of 129 was provided by analysis of the $^1$H NMR spectrum, which showed two 1H singlets at 6.88 and 6.86 ppm assigned as the fullerenyl protons of the diastereomeric mixture. While the amide protons appeared as a two broad singlets at 8.17 ppm (2H) and 8.14 ppm (1H). The presence of the ethyl ester was implied through the 2H quartet ($J = 6.5$ Hz) at 4.24 ppm, which was coupled (gCOSY) to a peak obscured by a large 9H singlet (1.44 ppm) assigned as the tert-butyl group. The $^{13}$C NMR spectrum showed a doubling up of peaks, which was consistent with the expected mixture of diastereomers. Confirmation of the structure was provided by examination of the ESI-MS, which showed a peak at $m/z$ 1274 assigned as the molecular ion (M+H$^-$).

![Scheme 2.11](image)

Scheme 2.11: The acyclic fullerenyl peptide 129 was synthesised through coupling of the fullerenyl amine 111a with the acid chloride 128.

This preliminary work suggests that the use of Fmoc amino acid chlorides in amide coupling reactions with fullerenyl glycinate 111a, to form fullerenyl peptides, has significant potential. Since this work was concerned with the establishment of synthetic methodology, the coupling with additional $N$-Fmoc protected amino acids, which was anticipated to be relatively straight-forward, was not investigated. Instead the synthesis pushed forward and Fmoc deprotection of 129 was attempted. Standard conditions for the
removal of Fmoc protecting group uses an amine base, \textit{e.g.} piperidine, which could potentially add to the electron deficient C\textsubscript{60} cage and/or abstract the fullerenyl hydrogen. It was expected that the steric bulk of the addend of 129 would protect the fullerenyl proton from deprotonation. While it was hoped that by doing the deprotection reaction in the absence of light and in a relatively non-polar solvent the addition of the amine, which is postulated to attack through a single electron transfer mechanism,\textsuperscript{54} would be slowed enough for a selective deprotection of 129 to occur. To prevent the addition of the amine through a singlet oxygen pathway,\textsuperscript{54} oxygen was also excluded from the reaction.

Therefore, a solution of the fullerenyl dipeptide 129 in degassed chloroform was treated with piperidine (2 equivs.) in the dark at RT for 3 h under an atmosphere of N\textsubscript{2}. Analysis of the reaction by TLC indicated the formation of a product, which possessed a lower \( R_f \) value than 129, speculated to be the free amine 130. A solution of Fmoc-phenylalanine (5 equivs.), which had been activated by EDCI/HOBt was then added to the reaction mixture along with solid NaHCO\textsubscript{3} and the suspension was stirred for 16 h (Scheme 2.12). Analysis of the crude material by ESI-MS indicated formation of the desired tripeptide 131 with a peak at \( m/z \) 1421 assigned as the molecular ion (M+H)\textsuperscript{+} of the tripeptide. Notably, a peak at \( m/z \) 1274 was also present corresponding to the protected dipeptide 129. With insufficient material available for further structural elucidation work, it can only be tentatively suggested that the tripeptide was present in the crude reaction mixture.
Scheme 2.12: The fullerenyl tripeptide 131 was accessed via Fmoc deprotection of 129 and in situ coupling with Fmoc-phenylalaninoyl chloride.

2.3.6 Attempts at Lewis acid mediated carboxyl deprotection of dihydrofullerenyl derivatives 99 and 123

In order to incorporate 123 into an amino acid sequence, deprotection of the carboxyl group was attempted using the Lewis acid BBr₃ (1.1 equivs.) in CH₂Cl₂, which was added to a solution of the ester 123 at 0 °C (Scheme 2.13). TLC analysis indicated the reaction conditions were too harsh with the molecule decomposing within 2 h. Within the
peptide 123, additional sites exist, which would coordinate to the vacant orbital of the boron atom. However it was thought that the BBr$_3$ would preferentially complex with the more electron rich carbonyl of the ester. Whilst this was a disappointing result it was thought possible to deprotect the carboxyl group on the less substituted dihydrofullerenyl derivatives 99a-b which presumably could then be coupled before attempting the amine deprotection and subsequent coupling (Scheme 2.13). Hence using analogous reaction conditions to that described above, solutions of 99a or 99b in CH$_2$Cl$_2$ were treated with BBr$_3$ however, TLC analysis again indicated degradation had occurred within 6 h.

![Scheme 2.13: Attempted synthesis of dihydrofullerenyl acids 132 and 133.](image-url)
2.3.7 Attempts to form fullerenylglycine

It was envisaged that the conditions for the reductive removal of the benzhydryl group (TFA/Et₃SiH) would also remove the acid labile tert-butyl ester of 99b providing fullerenylglycine (Fgly) 94 (Scheme 2.14).

![Scheme 2.14: Global deprotection of 99b to produce fullerenylglycine (Fgly) 94.](image)

Hence a solution of 99b was treated with TFA/Et₃SiH and the reaction mixture was stirred at 45 °C for 30 min. Upon exposure to these conditions the molecule degraded rapidly, with TLC analysis indicating the products to be pristine fullerene and baseline material. The insoluble (baseline) material was collected and subjected to ESI-MS analysis however no meaningful data was obtained. This was thought to be a result of the extreme insolubility of the product(s) formed. It was expected that 94 would have an extremely poor solubility profile and readily form aggregates. Hence the remaining solid was added to a solution of EDCI and HOBT in dry CH₂Cl₂ and the suspension was sonicated for 15 min before the addition of methyl phenylalaninate. It was hoped that if 94 was present in the mixture a small percentage of it would have dissolved into the solution and been available to undergo the peptide coupling. If this had been the case, an equilibrium would have existed pushing the reaction to completion. The reaction was monitored via TLC hourly, for 10 h, however no changes were observed. It is difficult to know if Fgly (94) was generated.
in the previous reaction and its poor solubility profile was hampering the amide coupling, or if this compound was unstable to the global deprotection conditions.

To investigate which reagent (Et₃SiH or TFA) was incompatible with 99b, a solution of 99b in CH₂Cl₂ was treated with TFA at RT, again an insoluble precipitate formed (Scheme 2.15). Analysis of the sample by ESI-MS provided no clues to its structural identity. The material was further subjected to standard amide coupling conditions however analysis of the crude mixture by TLC indicated no reaction had occurred. Attempts to remove the tert-butyl ester via hydrolysis with HCl also proved problematic with the formation of an insoluble product, which could be neither characterised nor functionalised. With the synthesis of the dihydrofullerenyl acid 133 proving problematic, which could not be readily overcome, this line of work was not further pursued.

**Scheme 2.15:** Attempted synthesis of dihydrofullerenyl acid 133.

### 2.3.8 Conclusions for Path A

In summary, the reductive removal of the benzhydryl group of 99a provided the novel ethyl α-fullerenyl glycinate 111a, the first α-substituted acyclic fullerenyl amino ester. This fullerenyl amino ester was shown to readily participate in intramolecular Mannich type reactions representing a new and potentially general method for access to
fulleropyrrolidines. Attempts to deprotect the carboxyl group in the dihydrofullerenyl derivatives 99a/b and 123 were unsuccessful, not allowing for the incorporation of fullereryl glycine into a peptide sequence but rather, in principal, providing a general method for the generation of peptides with the carboxyl end “capped” with ethyl α-fullerenylglycinate.

2.4 From Fullerenyldihydroprroles 106a/b To Fullerenyld Peptides 110 (synthetic path B)

In our attempts to prepare fullerenyld peptide derivatives (e.g. 110, Scheme 2.16) from the fullerenyldihydroprroles 106a-b the reverse sequence of chemical steps to that described in Section 2.4.1 was employed. The synthetic plan involved the initial introduction of the second amino acid moiety to the carboxylic acid 114, derived from 106a-b, using standard amide coupling methods followed by reductive ring-opening of the resultant dipeptide 115 as illustrated in Scheme 2.16. This would provide access to the dihydrofullerenyl derivative 116, which could potentially be converted to the amine 117, and coupled to an amino ester, using the established procedures (Sections 2.3.1 and 2.3.3), hence leading to the incorporation of Fgly into a peptide sequence of the general structure 110 (Scheme 2.16).
Scheme 2.16: Retrosynthetic analysis of 110 to the known fullerenyldihydropyrroles 106, the key step is the reductive ring-opening of the peptide 115 to form the α-fullerenyl peptide 116.

2.4.1 Fullerenyldihydropyrrole carboxylic acid

The fullerenyldihydropyrroles 106a-b were converted to the acid 114, with the most efficient method found to be the treatment of a solution of tert-butyl ester 106b in CH₂Cl₂ with TFA at RT for 3 h (Scheme 2.17). To the suspension was added hexanes and the precipitate collected providing the acid 114 in 60% yield. Alternatively, the ethyl ester 106a was dissolved in CH₂Cl₂ and treated with BBr₃ and the reaction mixture was stirred for 15 h at RT, before being quenched with water. The organic layer was then collected and concentrated under reduced pressure to provide the fullerenyl acid 114 as a brown solid in 28% yield.
Scheme 2.17: The esters 106a-b were converted to the fullerenyl acid 114, then coupled to ethyl phenylalaninate to form 115a.

Examination of the $^1$H NMR spectrum of 114 revealed the loss of the tert-butyl or ethyl resonances of 106b or 106a, respectively, along with the appearance of a broad singlet, with a relative integration of 1H, at 8.63 ppm attributed to the carboxylic acid proton. Confirmation of the structure of 114 was provided by analysis of the mass spectrum, which showed a base peak at $m/z$ 956 assigned as the molecular ion (M-H)$^-$. This was then mass selected and subjected to analysis by tandem mass spectrometry. The fragmentation pattern showed a loss of 44 amu ($m/z$ 912), which is characteristic of carbon dioxide, and a loss of 237 amu (the entire addend) to leave pristine fullerene ($m/z$ 720).
2.4.2 Amide coupling of carboxylic acid 114

Under EDCI/HOBt amide coupling reaction conditions, the fullerene acid 114 was found to readily couple to ethyl L-phenylalaninate in CH₂Cl₂ at RT in 30 min (Scheme 2.17). The solution was washed with water then the solvent was reduced in volume to approximately half before being applied directly to the top of a silica gel column. Elution with CH₂Cl₂ provided the fullerene peptide 115a in 62% yield. Evidence for the successful coupling was provided by analysis of the ¹H NMR spectrum of 115a which indicated loss of the resonance attributable to the carboxylic acid proton and the presence of a broad doublet, with a relative integration of 1H at δ 8.21 ppm, assigned as the amide proton. The presence of a stereogenic centre was evident with the characteristic shift and splitting of the benzyl protons (3.26 and 3.42 ppm both a doublet of doublets) next to the stereogenic centre of the L-phenylalanine moiety. Analysis of the ¹³C NMR spectrum of 115a indicated preservation of the diphenyldihydropyrrole ring with the characteristic resonance of the sp³ carbon of the pyrrole ring present at 95.4 ppm. The lack of symmetry was also clearly evident with 53 fullerene sp³ resonances observed (5 of these were coincidental overlaps i.e double intensity taking the total to the expected 58 resonances). The fullerene sp³ carbon resonances were present at 82.2 and 83.6 ppm, indicative of attachment to a pyrrole moiety.¹²⁸ Long-range ¹³C to ¹H correlations identified the aromatic quaternary carbons with the diphenyl ipso resonances overlapping at 141.4 ppm and the phenylalanine aromatic quaternary carbon resonance appearing further upfield at 137.7 ppm. Confirmation of the structure was provided by analysis of the ESI-MS with a peak at m/z 1133 assigned as the molecular ion (M+H)⁺.
2.4.3 Attempted addition of diphenyliminopeptides to fullerene under Bingel conditions

A potential way to shorten the number of synthetic steps involving fullerene, and increase the overall yield, was to synthesise the N-protected peptide first and then add it directly to fullerene under Bingel cyclopropanation reaction conditions (Scheme 2.18).

To this end N-Boc-glycine was coupled to methyl L-phenylalaninate under standard EDCI/HOBt coupling conditions providing the known dipeptide 134 in 63% yield (Scheme 2.16), which was spectroscopically identical to that reported in the literature.\textsuperscript{139}

\[
\text{H}_2\text{N}\xrightarrow{\text{EDCI/HOBt, NEt}_3, \text{CH}_2\text{Cl}_2} \text{O} \xrightarrow{63\%} \text{O} \xrightarrow{\text{H}_2\text{N}} \xrightarrow{\text{CO}_2\text{Me}} \xrightarrow{\text{Ph}} \text{N}_0\text{protected peptide}
\]

\[
\xrightarrow{\text{C}_6\text{O, DBU, CBr}_4, \text{toluene}} \text{N} \xrightarrow{\text{Ph}} \text{H} \xrightarrow{\text{NH}} \text{N} \xrightarrow{\text{Ph}} \text{H} \xrightarrow{\text{CO}_2\text{Me}} \xrightarrow{\text{Ph}} \text{N}_0\text{protected dipeptide}
\]

\[
\xrightarrow{\text{TFA}} \text{94\%}
\]

\[
\xrightarrow{\text{TFA}} \text{H}_2\text{N} \xrightarrow{\text{O}} \xrightarrow{\text{H}} \xrightarrow{\text{CO}_2\text{Me}} \xrightarrow{\text{Ph}} \text{N}_0\text{protected dipeptide}
\]

\[
\xrightarrow{\text{38\%}} \text{N} \xrightarrow{\text{Ph}} \text{H} \xrightarrow{\text{NH}} \text{N} \xrightarrow{\text{Ph}} \text{H} \xrightarrow{\text{CO}_2\text{Me}} \xrightarrow{\text{Ph}} \text{N}_0\text{protected dipeptide}
\]

Scheme 2.18: The attempts to add the N-protected dipeptide 136 to fullerene under Bingel cyclopropanation conditions were unsuccessful.

Removal of the Boc group of 134 was achieved by treatment with TFA providing the known dipeptide 135 in 94% yield (Scheme 2.18).\textsuperscript{139} However, to the best of our knowledge, no spectral data for this compound has been reported. Analysis of the $^1$H NMR spectrum supported the proposed structure of 135 with the resonance at 1.35 ppm, assigned as the tert-butyl group in 134, no longer being present. Further confirmation of the structure was provided by ESI-MS analysis, which showed a peak at $m/z$ 351 and was assigned as the molecular ion (M+H)$^+$. 
Transimination was achieved using an established method,\textsuperscript{108, 109} providing the known N-protected dipeptide \textbf{136} in 38\% yield.\textsuperscript{140} However, to the best of our knowledge, no spectral data for this compound has been reported. Therefore, analysis of the $^1$H NMR spectrum revealed a downfield shift of the resonance attributed to the acidic methylene protons of the glycine moiety, which shifted from 3.74 to 3.96 ppm and changed multiplicity from a quartet to a sharp singlet, clearly indicating the addition of the diphenylimino moiety. The aromatic chemical shift region in both the $^1$H NMR and $^{13}$C NMR spectrum showed additional signals indicating the addition of the diphenylimino moiety, while further downfield in the $^{13}$C NMR there was an emergence of a resonance at 171.8 ppm attributed to the carbon of the imine group. Confirmation of the structure was provided by ESI-MS analysis, which showed a peak at $m/z$ 401, which was assigned as the molecular ion (M+H)$^+$. 

Attempts to add the dipeptide \textbf{136} to [60]fullerene under standard Bingel conditions, \textit{i.e.} 1 equiv. of fullerene, 1.1 equiv. of \textbf{136}, 1.2 equivs of CBr$_4$, and 3.5 equiv. of DBU, only produced polymeric material and unreacted fullerene, as judged by TLC analysis. This remained the outcome despite lengthening reaction times.

\textbf{2.4.4 Attempted reductive ring-opening reactions on fullereryl peptide 115a and fullereryl acid 114}

In order to access the acyclic fullereryl peptide \textbf{116a} (Scheme 2.19), compound \textbf{115a} was subjected to the optimised reductive ring-opening conditions (entry 17, Table 2.3). Unfortunately no reaction was observed to take place with a near quantititative return of the starting material. It was speculated that the Lewis acid (BF$_3$.Et$_2$O) preferentially complexed with the peptide section of the molecule rather than, or in conjunction with, the
desired imino-activation. However, increasing the number of equivalents of Lewis acid did not result in conversion to the desired material but rather led to the generation of pristine fullerene and polymeric material. All efforts to achieve the dihydrofullerenyl peptide 116a via this method were unsuccessful.

Scheme 2.19: Efforts to ring-open 115a to form the dihydrofullerenyl derivative 116a were unsuccessful.

Reductive ring-opening was attempted on the fullerenyl acid 114, but again degradation of the starting material to fullerene and polymeric material was observed. Ring-opening and formation of the carboxylic acid in one pot was attempted on 106a, keeping the original conditions except using BBr₃ (instead of BF₃·Et₂O) as the Lewis acid to promote both the ring opening and de-ethylolation. TLC analysis indicated the presence of C₆₀, the ethyl ring opened product 99a, starting material and a large amount of base line material. It was expected that the desired dihydrofullerenyl acid 133 (Scheme 2.20) would be relatively polar and hence could be part of the base line material on the afore mentioned TLC. Analysis of the reaction mixture by ESI-MS suggested that formation of the dihydrofullerenyl acid had not occurred. Thus it also appears that access to fullerenyl amino acids through this pathway is problematic.
Attempts to ring-open the acid 114 were unsuccessful, likewise attempts to ring-open and form acid 133 from 106a in one pot were disappointing.

2.5 Conclusions

This chapter described the structural reassignment for the addition of diphenyliminoglycinates to [60]fullerene under Bingel cyclopropanation conditions, with these fullerenyldihydropyrroles serving as protected α-fullerenyl amino acids. Mechanistic details of the reductive ring-opening of the fullerenyldihydropyrroles were discussed along with a method to reductively remove the benzhydryl group to form ethyl α-fullerenylglycinate, the first reported acyclic α-substituted fullerenyl amino ester 111a (Path A). This was subsequently coupled to N-phthylglycine and \( N_\alpha\)-Fmoc-\( N_e\)-Boc-L-Lysinoyl chloride to form α-fullerenylidipeptides. Preliminary results indicate that the Fmoc group can be removed under standard basic conditions and subsequent EDCI/HOBt mediated amide coupling was successful in producing a tripeptide. Efforts to deprotect the carboxyl end of the dihydrofullerenyl derivatives were met with disappointment.

In path B, diphenylfullerenyldihydropyrroles 106a,b were converted to the corresponding carboxylic acid 114 and subsequently coupled to ethyl phenylalaninate.
Attempts to ring-open the pyrrole to gain access to the amine and allow for incorporation of the fullereryl amino acid into a peptide sequence were unsuccessful.
3.1 Generating methano[60]fullerenyl derivatives from the addition of iminoglycinates to fullerene

The synthesis and use of malonate derived methano[60]fullerenes in medicinal chemistry and material science is extensive.\textsuperscript{60, 64, 141, 142} It was anticipated that iminooester-based methano[60]fullerenyl derivatives of the type 97 would provide additional analogs to complement, compare and hopefully improve established useful properties, with the end goal being enhancement of the applications of methano[60]fullerenes to nanotechnology.

The rationale behind the formation of the diphenylfullerenyldihydropyrrole 106 over the methanofullerene 97 was thought to be the result of several factors (Scheme 3.1). The imino-carbon of the diphenylimine 96 is activated by the electron withdrawing nature of the aromatic rings, which additionally do not provide sufficient steric hinderance of the imine sp\textsuperscript{2} carbon (C\textsubscript{α}) to overcome attack from the fullerenyl anion. The driving force is two-fold; nucleophilic attack on an electron-poor imino carbon (C\textsubscript{α}), and formation of a more stable five-membered ring compared to the more strained cyclopropyl ring.

![Scheme 3.1](image)

\textbf{Scheme 3.1:} The addition of diphenyliminoglycinates 96 to fullerene under Bingel cyclopropanation conditions provided the diphenylidihydropyrroles 106 and not the previously reported 97.

In an attempt to achieve a cyclopropanation reaction between [60]fullerene and an iminoglycinate, thus affording methanofullerenyl amino acid precursors, various
iminoglycinates of the general structure 136 were synthesised (Scheme 3.2). It was thought that iminoglycinate derivatives that had less activation and/or more steric hinderance of the imino-carbon (C₆) would be more likely to provide the corresponding cyclopropyl derivative. Access to the iminoglycinates should be readily achieved by condensation of carbonyl containing compounds with glycines 137a-b, target compounds can be divided into 3 groups: 1) alkyl iminoglycinates; 2) thioiminoglycinates; and 3) aromatic iminoglycinates. Once synthesised, these iminoglycinates were added to fullerene under two different reaction conditions namely: a) the Bingel cyclopropanation reaction conditions; and b) under manganese(III) mediated radical addition reaction conditions.

![Scheme 3.2: Synthetic strategy to produce fullereny peptides 103.](image)

### 3.2 Alkyl iminoglycinates

The initial iminoglycinates were chosen to examine both the effect of not activating the imino-carbon (C₆, Scheme 3.3) and the effect of increasing the steric bulk from tert-butyl 138, to di-tert-butyl 139 and camphor 140 iminoglycinates. It was envisaged that the addition of these alkyliminoglycinates to fullerene under various reaction conditions would result in methano[60]fullerenyl derivatives.
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

Scheme 3.3: Alkyliminoglycinates to be synthesised.

3.2.1 Synthesis of ethyl N-(2,2-dimethylpropylidene)glycinate

The first iminoglycinate synthesised, 138 (Scheme 3.4), was generated by the condensation of pivaldehyde with ethyl glycinate. Magnesium sulfate was used to remove the emancipated water helping to drive the reaction to completion providing the known imine 138 in 82% yield, which was spectroscopically equivalent, and similar in yield, to that reported in the literature.\textsuperscript{143} Notably, a long-range coupling ($J = 1.2$ Hz) between the imine proton and the methylene protons of the glycinate was observed in the $^1$H NMR spectrum of 138, which was not previously reported.

Scheme 3.4: Synthesis of imine 138 in 82% yield.

3.2.2 Synthesis of ethyl N-(2,2’,4,4’-tetramethylpentylidene)glycinate

It was anticipated that access to the imine 139 (Scheme 3.5) through a condensation reaction of 2,2’,4,4’-tetramethylpentanone with ethyl glycinate would be unlikely due to the large steric bulk of the tert-butyl groups. Likewise, an imine exchange reaction with the commercially available imine 141 would also be affected by steric issues. Methods exist to
convert ketones to thio ketones,\textsuperscript{144} which are routinely used in the synthesis of sterically hindered imines.\textsuperscript{145} However, these are typically low yielding and require additional synthetic steps. Therefore, a solution of ethyl bromoacetate and anhydrous Na$_2$CO$_3$ in acetonitrile was treated with imine 141 and the reaction mixture was heated at 130 °C in a sealed tube for 48 h affording the novel iminoglycinate 139 in 73% yield.

\[
\text{NH} + \text{Br}\text{O}_2\text{O} \xrightarrow{\text{Na}_2\text{CO}_3, \text{MeCN}} 130 \degree\text{C, 48 h} \rightarrow \text{N}\text{O}\text{O}
\]

Scheme 3.5: The sterically hindered imine 139 was synthesised via a nucleophilic S$_{N}$2 displacement.

Analysis of the $^1$H NMR spectrum of 139 showed a 2H singlet at 4.48 ppm, which was assigned to the activated methylene protons. Additionally, the two tert-butyl groups no longer had identical chemical shifts (1.22 and 1.31 ppm) due to their cis/trans relationships relative to the carbonyl group of the ester, hence supporting the structural assignment. Analysis of the $^{13}$C NMR spectrum of 139 showed two downfield resonances at 171.4 and 181.5 ppm assigned as the carbonyl and imine resonances, respectively. Examination of the ESI-MS spectrum confirmed the structure with a peak at $m/z$ 228 assigned as the molecular ion. Notably, this compound degraded quickly and was used immediately in subsequent reactions after isolation.

The slightly nucleophilic imine 141 readily attacked ethyl bromoacetate at high temperature and pressure forming the desired novel compound 139 along with hydrobromic acid as a by-product. Hence, the addition of base was required to avoid protonation of 141 making it less nucleophilic. However, a potential competing reaction would be the
deprotonation of the starting bromo ester, which could then react with another ethyl bromoacetate molecule affording the α,β-unsaturated diketone 142 (Scheme 3.6). The use of the weak inorganic base Na₂CO₃ seems to have reduced this possibility, resulting in a good yield of 139.

Scheme 3.6: A potential side reaction is the formation of the α,β-unsaturated diketone 142.

3.2.3 Synthesis of camphor iminoglycinates

The sterically hindered camphorimines 140a/b were both synthesised from commercially available (1R)-(−)-thiocamphor (Scheme 3.7). A solution of the thiocamphor in toluene was treated with the free base of ethyl glycinate, accessed via bubbling ammonia through a suspension of the hydrochloride salt in chloroform, and a catalytic amount of Lewis acid (BF₃.(OEt)₂). The reaction mixture was then heated at reflux in toluene overnight, to provide the desired imine 140a albeit heavily contaminated with polyglycine. This had previously been observed, although the use of a Lewis acid to accelerate the reaction and limit polymerisation, had not been reported. The reaction of tert-butyl glycinate and thiocamphor proceeded smoothly upon heating a solution of equimolar quantities of both starting materials in toluene at reflux for 36 h to deliver the imine 140b in
85% yield. This compound was spectroscopically equivalent to that reported in the literature.\textsuperscript{145}

\[
\begin{array}{c}
\text{Skeletally hindered imine} \\
\text{Thioiminoglycinates}
\end{array}
\]

3.3 Thioiminoglycinates

Thioiminoglycinates were also examined with the known lability of the imine group in acidic media increasing their appeal.\textsuperscript{146} The two compounds targeted for synthesis were the dithiomethyliminoglycinate 143 and the dithiocyclohexyliminoglycinate 144 (Schemes 3.8 and 3.9).

3.3.1 Synthesis ethyl and tert-butyldithiomethylglycinate

The dithiomethylglycinate 143 (Scheme 3.8) was synthesised by the addition of CS\textsubscript{2} and Et\textsubscript{3}N to ethyl glycinate hydrochloride in anhydrous CH\textsubscript{2}Cl\textsubscript{2} to form the thiolate. This was then methylated \textit{in situ} forming the thioamide 145. Subsequent methylation required a longer reaction time and a stronger base to furnish the known volatile imine 143 in 63% yield along with the thioamide intermediate 145 (18%). Both products were spectroscopically identical to that reported in the literature.\textsuperscript{147} The analogous tert-butyl ester of 143 was accessed using a literature procedure.\textsuperscript{148}
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

Scheme 3.8: Synthesis of the dithiomethylglycinate 143.

3.3.2 Synthesis of dithiocyclohexylimine

The novel dithiocyclohexylimine 144 was synthesised through the treatment of ethyl glycinate in anhydrous CH₂Cl₂ with carbon disulfide and 1,3-dibromopropane in the presence of Et₃N (Scheme 3.9). The crude residue was then subjected to neutral alumina column chromatography, and elution with diethyl ether/hexanes (3:2) provided 144 as a pale yellow oil in 73% yield, with the reaction mechanism similar to that shown in Scheme 3.8.

Scheme 3.9: Synthesis of the dithiomethylglycinate 144.

Confirmation of the structure of 144 (Figure 3.1) was provided by analysis of its ¹H NMR spectrum, which showed a downfield singlet at 4.79 ppm, with a relative integration of 2H, indicative of the doubly activated methylene protons. Retention of the ethyl ester was implied through the relative integrations and multiplicities of the resonances at 4.20
ppm (2H, quartet) which were coupled to a triplet (3H, 1.26 ppm). The non-equivalence of the methylene protons adjacent to the sulfur atoms, *cis* (3.61 ppm) and *trans* (3.01 ppm), was also indicative of addition, with the *cis/trans* assignment based upon precedent of related chemical shifts found in the $^1$H NMR spectrum of dithiomethylimine 143. The non-equivalence of the methylene protons adjacent to the sulfur atoms was expected to arise from their *cis/trans* relationship relative to the carbonyl group of the ester (Figure 3.1). However, coupling of axial/equatorial protons adjacent to the sulfur atoms could also explain the $^1$H NMR spectrum, and cannot be discounted. The $^1$H to $^{13}$C correlations would have allowed for unambiguous characterisation, however the material was used in the following reactions before this could be acquired. Further evidence for the proposed structure was provided by examination of its $^{13}$C NMR spectrum that detailed two downfield resonances at 167.3 and 193.9 ppm assigned as the carbonyl and imine carbon resonances, respectively. ESI-MS analysis confirmed the structure with a peak at *m/z* 219 assigned as the molecular ion.

![Figure 3.1: $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 144.](image)
3.4 **Aromatic iminoglycinates**

The addition reactions of aromatic iminoglycinates to fullerene under various conditions were assessed. These compounds were not expected to afford cyclopropyl adducts under Bingel cyclopropanation reaction conditions due to the activation of the imino-carbon and lack of steric protection of the imine carbon from nucleophilic attack, as demonstrated in the diphenyliminoglycinate additions to fullerene. Since this chemistry had not been reported, and it offered the opportunity to further examine the structural features of iminoglycinates, which contribute to the reaction outcome with fullerene, a preliminary study was conducted.

3.4.1 **Synthesis of ethyl benzylideneglycinate**

The condensation of benzaldehyde with ethyl glycinate delivered the known benzylideneglycinate 146 in 98% yield, which was spectroscopically identical to that reported in the literature (Scheme 3.10).  

![Scheme 3.10: Condensation of benzaldehyde with ethyl glycinate afforded 146.](image)

3.5 **Bingel cyclopropanation reaction conditions**

To systematically investigate the factors that contributed to the type of reaction products from the addition of iminoglycinates to [60]fullerene under Bingel reaction conditions, the alkyl iminoglycinates were examined. Although alkyl imines do not activate the methylene position to deprotonation as well as the diphenylimine group they also do not
activate the imino carbon to nucleophilic attack, hence increasing the probability for the formation of a three-membered ring. The decrease in acidity of the methylene protons in \textbf{138-140} was expected to be easily overcome, if necessary, by the addition of a stronger base.

3.5.1 Addition of ethyl \textit{N-}(2,2-dimethylpropylidene)glycinate to [60]fullerene under Bingel conditions

To a solution of [60]fullerene, carbon tetrabromide and the imine \textbf{138} in toluene was added DBU dropwise. The reaction mixture was stirred at RT for 16 h before the crude material was subjected to flash silica gel chromatography. Elution with CH$_2$Cl$_2$/hexanes (1:1) led to the isolation of two bands. The most abundant compound was identified as the novel \textit{cis}-fulleropyrrolidine \textbf{121} in 29\% yield.

![Scheme 3.11: Under Bingel cyclopropanation conditions the imine \textbf{138} added to fullerene producing three adducts \textbf{121}, \textbf{147-8}.](image)

Evidence for the structure of the fulleropyrrolidine \textbf{121} was provided by analysis of its $^1$H NMR spectrum, which indicated the loss of the resonances corresponding to the imine proton (7.48 ppm) and the activated methylene protons (4.06 ppm) of the iminoglycinate \textbf{138}. Two downfield doublets each with relative integrations of 1H, at 4.59
and 5.42 ppm were assigned as H_a and H_c, respectively (Scheme 3.11). Both of these protons were found to couple (gCOSY) to a broad triplet at 3.72 ppm ($J = 14.0$ Hz) also with an integration of 1H (NH_b). Examination of the ROESY spectrum of 121 revealed cross-peaks between the tert-butyl group and H_a. Additional cross-peaks between H_a and H_c (Scheme 3.11) confirmed the structure of the fulleroypyrrolidine as the cis isomer. Analysis of the $^{13}$C NMR spectrum revealed 53 of the 58 fullerenyl sp$^2$ resonances and two sp$^3$ fullerenyl resonances at 78.8 and 79.8 ppm. Confirmation of the structure was further provided by ESI-MS analysis with a peak at m/z 891 assigned as the molecular ion (M$^+$).

Compound 121 was expected to arise from a base assisted cycloaddition of the imine 138 to C$_{60}$. To test this hypothesis a solution of fullerene and 138 in toluene was treated with DBU, in the absence of CBr$_4$, providing the cis-fulleroypyrrolidine 121 in 64% yield. The observed cis stereoselectivity was from addition of the trans-trans form of the imine A rather than the more sterically crowded cis-trans anion B (Scheme 3.12).

**Scheme 3.12**: Conformation A is likely to be energetically more favourable than conformation B, explaining the observed stereoselectivity upon addition to the fullerene cage.

Analysis of the $^1$H NMR spectrum of the other isolated band indicated it contained two products speculated to be the methanofullerene 147 and the dihydropyrrole 148. Key signals in the $^1$H NMR spectrum suggesting the structures of 147 and 148, were the singlet at 8.43 ppm assigned to the imino-proton (H_d) in the methanofullerene compound 147 (Scheme 3.11). Further upfield was an additional singlet (5.90 ppm) and this was assigned
to the methine proton $\alpha$ to the tert-butyl group ($H_e$) of 148. While 121 could be purified through silica gel chromatography, the separation of 147 and 148 was not possible as these compounds had the same retention time on silica gel in a variety of solvent systems. As described in next section (3.4.1.1), through manipulation of the Bingel reaction conditions, the ratio of the products (121, 147 and 148) from the addition of 138 to [60]fullerene were significantly altered facilitating the full characterisation of both compounds 147 and 148.

The best result achieved in terms of maximising the ratio of 147 : 148 was found to be from treatment of a solution of 138 and $C_{60}$ in toluene at 0 °C with CBr$_4$ (10 equiv.) and DBU (3 equiv.) providing 147 in 13% yield along with traces of 121 and 148. Figure 3.2 shows a $^1$H NMR spectrum of 147, which contains the fullerényldihydropyrrole 148 (~20%) as an impurity. Despite numerous recrystallisations of this mixture, the level of purity of 147 could not be further enhanced. Analysis of the $^1$H NMR spectrum revealed a downfield shift of the imine proton from 7.48 ppm in 138 to 8.43 ppm in 147 indicative of its close proximity to the fullerene cage in the later compound. The loss of the resonance corresponding to the methylene protons (4.06 ppm) of 138 also supported the structure of 147.
Figure 3.2: $^1$H NMR (500 MHz, CDCl$_3$/CS$_2$; 2 : 3) spectrum of methanofullerene 147. $H_e$ represents the resonance attributed to the fullerenyldihydropyrrole 148 side-product, which account for 20%, as determined by relative integrations. $X$ denotes CHCl$_3$ resonance.

Examination of the $^{13}$C NMR spectrum of 147, which contained 20% of 148 (Figure 3.3), revealed the presence of a plane of symmetry with 26 fullerienyl sp$^2$ and 1 sp$^3$ resonances indicating that the symmetry plane bisects the substitution site. This was indicative of a cyclopropyl analogue as no symmetry plane would exist for an unsymmetrical saturated or unsaturated five-membered ring fullerene adduct. The crowded fullerienyl sp$^2$ resonances (140-146 ppm) also supported the presence of the cyclopropyl functionality, along with the chemical shift of the resonance attributed to the fullerienyl sp$^3$ carbons (76.2 ppm). This crowded fullerienyl sp$^2$ chemical shift region (140-146 ppm)
was also observed for the methano[60]fullerenyl derivative 180, see Section 3.12.2 for details. Further downfield, a resonance at 181.5 ppm appeared and was assigned as the imine carbon (C_d), its relatively larger peak height, compared to the carbonyl resonance (C_f) at 164.2 ppm, indicated that this carbon was attached to a proton. This was confirmed by analysis of the HSQC spectrum, which showed the resonance at 181.5 ppm was attached to the downfield proton in the ^1H NMR spectrum assigned as the imine proton (8.43 ppm).

![Figure 3.3: Downfield region of the ^13C NMR spectrum (75 MHz, CDCl₃/CS₂; (2 : 3)) of 147.](image)

The instability of both 147 and 148 hampered purification efforts with significant degradation observed upon further purification of this mixture, with both compounds found to be acid sensitive. In order to obtain sufficient material to run multiple 2D NMR experiments purification was kept to a minimum, which meant that the sample contained both the cyclopropyl 147 and dihydropyrrole 148 fullerenyl derivatives. Since both compounds were synthesised as mixtures in various ratios, it was possible to assign individual resonances to specific compounds.

Examination of the HMBC spectrum of a 3 : 2 mixture of the methanofullerene 147 and the fullerenyldihydropyrrole 148 (Figure 3.4), respectively, showed a clear correlation from the imine proton (H_d) of 147 (8.43 ppm) to the quaternary and methyl carbons of the
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

tert-butyl group along with correlations to the bridgehead carbon (C₆) at 67.1 ppm and the fullerenyl sp³ carbons at 76.2 ppm. Analysis of the ESI-MS spectrum indicated a peak at m/z 889, that was tentatively assigned as the molecular ion (M⁺). It should be acknowledged that the sample subjected to ESI-MS analysis contained traces of the dihydropyrrole 148, which possess the same molecular formulae and cannot be discounted as being the source of this peak.

![Diagram](image)

**Figure 3.4:** HMBC spectrum (600 MHz, CDCl₃/CS₂/toluene) of a 3 : 2 mixture of compounds 147 and 148, respectively.

When the imine 138 was subjected to Bingel cyclopropanation reaction conditions with C₆₀ in toluene at 50 °C, the dihydropyrrole 148 was isolated in 17% yield with no traces of 121 or 147. The characterisation of 148 was achieved by analysis of its ¹H NMR
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

spectrum (Figure 3.5). The most downfield proton was a singlet at 5.90 ppm with a relative integration of 1H, which is characteristic of the proton attached to the dihydropyrrole ring. The 2H quartet at 4.45 ppm was coupled to an upfield 3H triplet at 1.26 ppm assigned as the ethyl ester resonances, while the sharp 9H singlet at 1.63 ppm was assigned to the tert-butyl group.

![Figure 3.5: 1H NMR spectrum (300 MHz, CDCl3/CS2) of the dihydropyrrole 148, X denotes H2O resonance, while X and X denote the CH2Cl2 and CHCl3 resonances, respectively.](image)

Analysis of the HSQC spectrum of compound 148 indicated that the α-proton to the tert-butyl group (H_e, Figure 3.5) was attached to the carbon at 95.2 ppm, characteristic of the dihydropyrrole sp3 carbon. Examination of the HMBC spectrum (containing both 147 and 148 (Figure 3.4)) showed correlations from the proton attached to the dihydropyrrole ring (H_e) to the fullerene cage itself, including correlations to the two fullerrenyl sp3 resonances at 75.4 and 83.3 ppm, whilst the cross-peaks to the resonances at 25.5 and 38.6 ppm were attributed to the methyl and quaternary carbons of the tert-butyl group,
respectively. Confirmation of the structure was provided by analysis of the ESI-MS spectrum with a peak at $m/z$ 889, which was assigned as the molecular ion (M⁻).

It was possible that the pyrrolidine 121 was the precursor to the dihydropyrrole 148. This would be expected to occur via in situ bromination of 121 forming 149, which could be deprotonated by DBU, with collapse of the anion and loss of the bromide ion generating 148 (Scheme 3.13). To examine this possibility, a solution of the fulleropyrrolidine 121 in toluene was treated with CBr₄ (1.2 equiv.) and DBU (4 equiv.) (i.e. under Bingel reaction conditions) and the reaction was stirred overnight at RT. TLC analysis indicated the presence of the starting pyrrolidine and traces of C₆₀. Thus it appeared that the mechanism for the formation of 148 did not proceed through fulleropyrrolidine 121. It is likely that the steric constraints provided by the fullerene cage in 121 were too large to allow the DBU to abstract the methine proton α to the ester.

Scheme 3.13: The pyrrolidine 121 is not an intermediate in the synthesis of the dihydropyrrole 148.
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

While the mechanism for the formation of 148 is most likely similar to that described in Scheme 2.2 an alternative mechanism is shown in Scheme 3.14. Whereby formation of the dihydropyrrole 148 occurs through addition of the addend 138 to the fullerene cage before *in situ* bromination of the fulleropyrrolidine amine anion 150 (Scheme 3.14) in the first irreversible step of the reaction sequence. However, the bromo-derivative 151 would still require proton abstraction of the sterically hindered methine proton α to the ester to form the dihydropyrrole 148 (Scheme 3.14).

![Scheme 3.14: Possible mechanisms for the formation of the dihydropyrrole 148.](image)

3.5.1.1 Manipulating the reaction conditions to alter product outcome

In order to fully characterise the mixture of the methano and dihydropyrrole fullerenyl derivatives 147 and 148, we required a method to synthesis both independently or, at least a method to vary their ratio. Hence a systematic study looking at the effect the number of equivalents of reagent(s) added and reaction temperature had on the product
outcome was conducted (Table 3.1). As described in the previous section the Bingel
cyclopropanation reaction conditions could be tailored such that 147 would appear as a
major product and conversely manipulated such that only the dihydropyrrole 148 was
isolated. What was not discussed was the preliminary experiments done to achieve this
result.

As shown in Table 3.1, increasing the molar equivalents of the brominating agent
(CBr₄) led to a decrease in the yield of the pyrrolidine 121 which arises from a
cycloaddition of 138 to C₆₀ before the in situ bromination, and an increase in formation of
both the fullerencyldihydropyrrole 148 and cyclopropyl 147 derivatives which presumably
results from addition of the brominated iminoglycinate to the fullerene cage or from
bromination of intermediate 150 (Scheme 3.14).

**Table 3.1**: Addition of 138 to fullerene under Bingel conditions provided three products.

<table>
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<th>Entry</th>
<th>DBU (equiv.)</th>
<th>CBr₄ (equiv.)</th>
<th>Temp (°C)</th>
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<th>147 (%)</th>
<th>148 (%)</th>
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<td>trace*</td>
</tr>
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</table>

*Trace indicates <10% of the total purified products
Increasing the reaction temperature lead to an increase in yield of the five-membered ring product 148 compared to the three-membered ring product 147. The steric blocking of the tert-butyl group appeared to limit nucleophilic attack on the imine carbon, however this was lessened with increasing reaction temperature. Conversely, decreasing the reaction temperature from RT to 0 °C lead to an increased ratio of the cyclopropyl adduct 147 compared to the dihydropyrrole adduct 148 (entries 7-9, Table 3.1). The reaction proceeded at low temperatures (0 °C) however, as expected, required longer reaction times to reach completion (from 12 h to 18 h). As a result of lowering the temperature it was envisaged a stronger base might be required to deprotonate the activated methylene carbon, however DBU was found to be sufficiently basic to abstract the methylene protons. Increasing the quantity of reagents beyond that shown in Table 3.1 led to an increase in degradation products and a greater difficulty in isolation of the products.

To summarise, a potentially general and mild method for the synthesis of the fulleropyrrolidine 121 was discovered. The dihydropyrrole derivative 148 can be synthesised as the sole product in 17% yield (entry 5), while the analogous cyclopropyl derivative 147 could not be synthesised as a sole product, the reaction could be tailored such that 147 was obtained containing approximately 10% of the dihydropyrrole 148 (entries 7-9).

### 3.5.2 Addition of ethyl N-(2,2’,4,4’-tetramethylpentylidene)glycinate to [60]fullerene under Bingel cyclopropanation reaction conditions

When the tert-butyl imine 138 was treated with C$_{60}$ under Bingel cyclopropanation reaction conditions a mixture of the cyclopropyl 147 and dihydropyrrole 148 adducts were isolated (Section 3.5.1). Thus it was expected that upon addition of the more sterically
hindered imine 139 to fullerene under Bingel reaction conditions that only the cyclopropane derivative would be observed.

The imine 139 (1.2 equiv.) was added to a solution of C_{60} (1 equiv.) and CBr\textsubscript{4} (5 equiv.) in freshly distilled toluene in a flame-dried, two-necked flask covered in Al foil and under an atmosphere of argon (Scheme 3.15). To this was added DBU (3.5 equiv.) dropwise and the reaction mixture was stirred for 12 h before the reaction was quenched with water, and the organic fraction collected and concentrated at RT. The crude residue was then applied to a flash silica gel column, which had been covered in Al foil. Elution with CH\textsubscript{2}Cl\textsubscript{2}/hexanes (1 : 1) and 0.5% (v/v) Et\textsubscript{3}N provided a brown solid, which was collected, stored under an atmosphere of argon and protected from the light.

\begin{equation}
139 \quad \xrightarrow{C_{60}, CBr_4, DBU, toluene} \quad 152a \quad ?
\end{equation}

\begin{equation}
139 \quad \xrightarrow{C_{60}, CBr_4, DBU, toluene} \quad 152b \quad ?
\end{equation}

**Scheme 3.15**: The addition of imine 139 to [60]fullerene under Bingel reaction conditions provided an unstable compound, speculated to be 152a.

Analysis of the \textsuperscript{1}H NMR spectrum indicated successful addition of 139 to C\textsubscript{60}, with the loss of the resonance attributed to the activated methylene protons of 139 (4.48 ppm), while the cis/trans tert-butyl resonances merged into one singlet (1.27 ppm) with an integration of 18H relative to the downfield CH\textsubscript{2} of the ethyl ester (4.25 ppm). The equivalence of the tert-butyl groups could be explained by the presence of a symmetry plane, which bisects them. Clearly such symmetry would exist in structure 152b (Scheme 3.15). The cis/trans geometry of the tert-butyl groups relative to the carbonyl group in 139
could potentially be conserved in 152a, if this was the case, the $^1$H NMR spectrum would be expected to show two resonances, one for each tert-butyl group, suggesting the reaction product is 152b. However, it is possible that the π bond of the imine was interacting with the C$_{60}$ cage, which could potentially weaken the imine bond allowing for faster interconversion of the tert-butyl groups via rotation about the (’Bu)$_2$C-N bond. Based on this possibility the structure 152a could not be ruled out.

Unfortunately, 152 was unstable and within a few hours the compound precipitated out of the deuterated NMR solvent and could not be re-dissolved in any organic solvent. This degradation process was clearly shown in the $^{13}$C NMR spectrum over time with the emergence of additional peaks. The large signal strength from the two equivalent tert-butyl groups allowed for long-range proton to carbon correlations (HMBC) to be observed in a relatively short time, which was crucial due to the instability of the product. Analysis of the HMBC spectrum detailed a strong correlation from the protons of the tert-butyl groups (H$_a$) to a resonance at 43 ppm, assigned as the quaternary carbon of the tert-butyl groups (C$_b$). The 3-bond correlation from H$_a$ to C$_a$ occurred because H$_a$ was correlating to a different C$_a$ than the one it was attached to, so it had the same chemical shift but a long-range small coupling. Another strong correlation to a downfield resonance at 183 ppm was observed which is characteristic of an imine resonance. Additionally a clearly visible, but weaker, correlation from these tert-butyl groups to a resonance at 65 ppm, which was assigned as the bridge-head carbon C$_d$ (Figure 3.6). Such correlations would be expected for structure 152a. Compound 152b can be considered unlikely as no correlation from the tert-butyl resonances to any resonances between 90-95 ppm, which is a characteristic chemical shift region of the sp$^3$ carbon of the dihydropyrrolo moiety, was observed. Additionally, the
Chapte\text{r 3: Synthesis and Addition of N-protected Amino Acids to Fullerene}

imine resonances of the structurally similar \textit{tert}-butyldihydropyrrole 148 and diphenyldihydropyrrole 106a were located at 159 ppm and 160 ppm, respectively, in the $^{13}\text{C}$ NMR spectrum (as determined by long range $^1\text{H}-^{13}\text{C}$ correlations). It is unlikely that this slight structural difference would account for such a large difference in chemical shift (183 ppm in 152a), further supporting the proposed methano[60]structure 152a. Since incomplete spectral data was obtained on this unstable derivative it can only be tentatively assigned as the methanofullerene 152a.

\textbf{Figure 3.6:} HMBC spectrum (500 MHz, CDCl$_3$/CS$_2$, (1:1)) of suspected methanofullerenyl adduct 152a.

It has been found that the yield of 152 could be improved through the addition of a large excess of brominating agent. It does however come at the cost of increasing the
difficulty in purification. This low yielding reaction, which formed unstable products, was not further pursued.

3.5.3 Bingel cyclopropanation addition of tert-butyl camphoriminoglycinate to fullerene

In an attempt to generate a more stable fullerenyl derivative, whilst still retaining the necessary bulky alkyl features to produce cyclopropyl[60]fullerene derivatives, a solution of the sterically hindered camphor-imine 140b (1.2 equiv.), [60]fullerene (1 equiv.) and CBr₄ (10 equiv.) in chlorobenzene was treated with DBU (3.5 equiv.) and the reaction was stirred for 72 h before the mixture was filtered and concentrated (Scheme 3.16). TLC analysis indicated the formation of two products, however the overall yield was poor (< 5%). The crude reaction mixture was filtered through a short plug of silica gel to remove the unreacted fullerene and baseline material. Analysis of the ¹H NMR spectrum of the crude mixture indicated that addition to the fullerene cage may have occurred with the resonance attributed to the methylene protons at 3.90 ppm of 140b no longer present. However the mixture contained at least two compounds, evident by two strong singlet resonances at 1.46 and 1.51 ppm, with different relative integrations, assigned as tert-butyl protons. Further purification via column chromatography provided two discreet bands. However, the first band contained at least two compounds, again suggested by the two peaks in the ¹H NMR spectrum attributed to tert-butyl groups, which changed in ratio after each purification step. These compounds were thought to be the methanofullerene 153a and dihydropyrrole 153b derivatives (Scheme 3.16). Analysis of the ¹H NMR spectrum of the second band indicated that it contained none of the characteristic peaks associated with
either of the afore mentioned structures. Due to the small quantity and low stability of this mixture no further spectroscopic information could be obtained.

![Scheme 3.16](image)

**Scheme 3.16**: Addition of the camphoriminoglycinolate 140 to fullerene under Bingel reaction conditions provided two unknown compounds speculated to be fullerrenyl derivatives 153.

It was found that by increasing the reaction temperature (RT to 70 °C) and the quantities of CBr₄ (10 equiv.) and DBU (10 equiv.) that these reactions proceeded at an enhanced rate (90 min). Analysis of the crude reaction mixture by TLC indicated significant conversion to two products with similar retention values to the products from the original reaction, along with large quantities of baseline material. Attempts to isolate these compounds were thwarted after the crude mixture was applied to a silica gel column and no compounds were eluted despite increasing solvent polarity from CH₂Cl₂/hexanes (1:1) to methanol (5%) in CH₂Cl₂. It has been previously reported, that at elevated temperatures DBU can add to the C₆₀ cage; since the reaction conditions were at elevated temperatures and contained a large excess of DBU this was also a possible explanation for the unwanted products.

The reaction was attempted again at 50 °C under the identical conditions reported above except DBU (4 equiv.) was added in 1 h intervals in a bid to maintain the rate and extent of the formation of the compounds of interest while hopefully avoiding the
associated purification problems and potential side products. Monitoring the reaction by TLC indicated no product formation after 2 h. The reaction was then heated at 60 °C for another 2 h before another 4 equiv. of DBU was added. Analysis of the reaction mixture by TLC after 6 h indicated a small quantity of the products had formed with most of the fullerene consumed and converted to baseline material. The reaction was then left for another 2 h before being left at RT overnight. The reaction was repeated several times with further manipulation of the reaction conditions, but despite these attempts no significant amount of the fullerényl derivative was ever isolated.

3.5.4 Dithioiminoglycinate addition to C$_{60}$

The lack of success experienced with the addition of alkyliminoglycinates to fullerene prompted the examination of alternative iminoglycinates that would hopefully overcome the stability and selectivity issues experienced with the alkyliminoglycinates. To this end, the use of thioiminoglycinates as precursors to methano[60]fullerenyl derivatives was explored. A previous worker in our laboratory had attempted the addition of the ethyl ester 143 to fullerene under Bingel reaction conditions without success.$^{149}$

Several problems exist with using the volatile addend 143, namely its noxious vapours and its difficult purification. To help minimise these problems the less volatile tert-butyl ester 154 was synthesised using a straightforward literature procedure.$^{148}$ The easier to work with imine 154 (Scheme 3.17) was then subjected to Bingel reaction conditions. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy indicated that addition to the fullerene cage may have occurred due to a loss of the signal for the activated methylene group (4.15 ppm) of 154. The poor yield and general instability of the product lead to
termination of attempts to isolate and characterise this adduct. However, the potential of using thioimines as nitrogen protecting groups still required further examination.

\[
\text{MeS} \quad \text{N} \quad \text{O} \quad \text{Et} \quad \overset{\text{C}_{60}, \text{CBr}_4, \text{DBU, toluene}}{\xrightarrow{\text{x}}} \quad \text{MeS} \quad \text{N} \quad \text{O} \quad \text{Bu}
\]

**Scheme 3.17:** The addition of the thioimine 154 to fullerene under Bingel cyclopropanation conditions produced an unstable compound.

### 3.5.5 Addition of dithiocyclohexylimine to [60]fullerene under Bingel cyclopropanation reaction conditions

Attempts to add the thioglycinate derivative 144 to [60]fullerene under Bingel cyclopropanation reaction conditions, again appeared to provide a fullerenyl derivative however the compound was unstable to both laboratory light and heat and degraded upon work-up. Analysis of the crude reaction mixture by \(^1\)H NMR spectroscopy provided no useful information. At this point the synthesis of thio-containing imines was no longer examined as addends for the addition to fullerene under Bingel cyclopropanation reaction conditions.

### 3.5.6 Synthesis of ethyl benzylideneglycinate and the addition to fullerene under Bingel cyclopropanation conditions

To further examine the structural features of iminoglycinates which contribute to the reaction outcome, compound 146 was treated with [60]fullerene under Bingel reaction conditions. This provided the fulleropyrrolidine 155 in 53% yield and as a 4 : 1 mixture of
cis and trans stereoisomers (Scheme 3.18). Both these isomers have been reported,\textsuperscript{150} and were synthesised by the addition of the imine 146 to a solution of fulleren in toluene which was then heated at reflux for 24 h to provide 155 in a 35% yield and as a 2 : 1 mixture of cis and trans stereoisomers.\textsuperscript{150}

Notably, the dihydropyrrole 156 was not observed under the Bingel cyclopropanation reaction conditions indicating that the cycloaddition of 146 to afford 155, was occurring at a faster rate than the in situ bromination of 155, which would presumably add to C\textsubscript{60} to form the dihydropyrrole 156 (Scheme 3.18). Alternatively, the bromination of the pyrrolidine anion 157 was not occurring which could have also potentially lead to the formation of 156.

Under optimised conditions compound 146 was found to undergo a base assisted cycloaddition with fullerene forming the corresponding fulleropyrrolidine 155 in 68% yield (4 : 1 cis/trans) with the isomers readily separable via column chromatography. Repeating the reaction in the presence of the relatively weak Lewis acid, LiBr, did not influence the ratio of stereoisomers or the overall yield.
Scheme 3.18: The addition of the aromatic iminoglycinate 146 to fullerene under various conditions provided the fulleropyrrolidine 155 as a mixture of the cis and trans stereoisomers.

3.6 Examination of the Bingel cyclopropanation reaction conditions

In order to extend these procedures to the synthesis of higher ordered structures for example, bis and trisadducts, we required a robust and at least moderate yielding reaction. Embarking upon any attempts to further substitute the [60]fullerene cage typically results in a significant loss in yield proportional to the number of additional substitutions to the fullerene cage.\(^{128}\) Possible reasons for the low yields experienced include incomplete \textit{in situ} bromination of 138 to give 158 (Scheme 3.19) and the reversible nature of the addition to the fullerene cage. Hence with this in mind, work was done to examine and improve the bromination of the iminoglycinates, with the end goal being the development of a robust
protocol for the synthesis of multifunctionalised methano[60]fullerenyl derivatives from iminoglycinates.

Scheme 3.19: Plausible pathways for the formation 121, 147 and 148.

To examine the extent of bromination of 138, this compound was subjected to Bingel reaction conditions, (5 : 6 : 5 molar equivalents of 138, CBr₄ and DBU, respectively) in the absence of [60]fullerene. The extent of bromination, that is conversion to 158, was determined by analysis of the ¹H NMR spectrum of the crude reaction mixture, which revealed the amount of 158 to be 6.8% with over 90% of the starting imine 138 still remaining (δ 6.64 ppm, CHBr of 158). By increasing the molar equivalents of CBr₄ to 5 equiv. the conversion to the α-bromoimine 158 was about 10% (¹H NMR). Interestingly, when the Bingel reaction was performed on 138 in the presence of fullerene with CBr₄ (5 equiv.) only 5% of the fulleropyrrolidine 121 was isolated, along with the cyclopropyl 147
and dihydropyrrole 148 fulleranyl derivatives isolated as a 5 : 4 mixture of 147 : 148, respectively, in 15% overall yield, suggesting that the in situ bromination of 138 was occurring before the addition to the fullerene cage.

Further work on trying to synthesise the α-bromoimine 158 showed that the addition of a large excess of carbon tetrabromide (> 10 equiv.) and DBU (10 equiv.) in CH₂Cl₂ at reflux was not sufficient for complete bromination, with typically only about 10% of 138 being brominated. This suggested that an equilibrium existed between enolate A and 158, which could arise from the debromination of 158 by the carbon tribromide anion (Scheme 3.19).

Efforts to isolate the bromo-derivative 158, via silica gel column chromatography, were unsuccessful with the imine groups of both 138 and 158 readily cleaved by the acidity of the silica gel. Treatment of the silica gel with Et₃N slowed the hydrolysis of the imine moieties of 138 and 158, however due to their similar retention times, in a variety of solvents, 158 could not be isolated without contamination with 138.

Bromination of 138 using NBS was also attempted but again was unsuccessful with uncharacterisable products being formed despite using one molar equivalent of this brominating agent over a wide range of temperatures (~78 °C to RT).

In conclusion, despite several attempts the bromination of imine 138 could not be achieved in considerable yields (> 10%). It is not clear at this stage whether the reason for the poor yields can be attributed to the bromination of the addend step, or if the poor yields could be overcome by the use of more reactive halogenating reagents (e.g. I₂). Imine brominations and additions to fullerene were not examined further due to the limited success and time restraints. Instead focus was shifted to the addition of alternatively
activated protected amino acids to [60]fullerene to produce methano[60]fullerenyl amino acids.

### 3.7 Summary/conclusions

The labile nature and the poor yields of the fullerenyliminoc adducts (with the exception of the well studied diphenyliminoglycinates, see Chapter 2) thus far, excluded them from any attempts to further the synthesis beyond mono-additions. It is clear that the halogenation step was problematic in terms of overall yield and despite considerable efforts no α-bromoiminoglycinate could be isolated. Possibly more frustrating was the instability of all fullerenyl-methano and dihydropyrrroles isolated. Future directions would include the examination into using more reactive halogenating reagents (for example I$_2$ or NIS) encompassed within an aromatic-alkyliminoglycinate like 160 (Scheme 3.20). Which could potentially be more stable (based on the diphenylimino case), whilst also providing the necessary steric bulk to limit nucleophilic attack at the imine carbon.

![Scheme 3.20: A future iminoglycinate to be synthesised](image)

### 3.8 Reductive ring-opening reaction on a mixture of 147 and 148

To examine the scope of the reductive ring-opening, a 1 : 1 mixture of 147 and 148 was subjected to the standard reductive ring-opening conditions (Section 2.2.1), however the addition of acid to quench the proposed anionic intermediate was avoided, due to the
previously observed labile nature of the starting materials in acidic media. TLC analysis indicated the starting materials had been consumed 45 min after the addition of the reducing agent. Purification via silica gel column chromatography provided two compounds; one was found to be the known cis-pyrrolidine 121, while the other was identified as the novel ring-opened derivative 161 (Scheme 3.21).

Scheme 3.21: A 1:1 mixture of the dihydropyrrole 148 and cyclopropyl 147 was subjected to reductive ring-opening conditions, the pyrrolidine 121 and dihydrofullerenyl 161 were isolated.

The structure of the dihydro[60]fullerenyl ester 161 was determined by analysis of its $^1$H NMR spectrum (Figure 3.7), which showed a singlet at 7.02 ppm, with a relative integration of 1H, indicative of the fullerenyl proton (H$_c$). The proton attached to the stereogenic carbon (H$_a$) appeared at the characteristic chemical shift of 4.96 ppm. Further upfield the resonances of the diastereotopic methylene protons H$_{b/b'}$ appeared at 2.76 (d, $J$ = 9.5 Hz) and 3.03 (d, $J$ = 9.5 Hz) ppm. This connectivity was confirmed by analysis of the HSQC spectrum, which indicated that both protons with resonances at 2.76 and 3.03 ppm were connected to the same carbon at 61.7 ppm. Analysis of the long-range couplings showed a 3-bond correlation from H$_c$ to C$_a$. Further confirmation of the structure was
provided by examination of the ESI-MS spectrum, which showed a peak at \( m/z \) 894 assigned as the molecular ion (M+H)⁺.

![Figure 3.7: \(^1\)H NMR (500 MHz, CDCl\(_3\)/CS\(_2\), (6 : 4)) spectrum of 161.](image)

In order to unequivocally determine the origins of 121 and 161 from the above reaction, the reductive ring-opening of the dihydropyrrole 148, which was synthesised using the previously described procedure (Table 3.1, entry 5) was examined. This provided the known cis fulleropyrrolidine 121 in 76% yield, with no indication of the formation of 161. The absence of the trans isomer was expected to arise from the bulky tert-butyl group blocking the hydride attack from that face, hence only the cis isomer was observed. Thus, by inference, the methano[60]fullerene 147 undergoes reductive ring-opening to provide the novel dihydrofullerene 161. It was presumed that the fullerenylidihydropyrrole 148 did not ring-open to form 161, unlike the analogous diphenylfullerenylidihydropyrrole, due to reduced conjugation (stabilisation). That is, the imine moiety of the intermediate 162 is far
less stable, compared to that for the corresponding diphenyl iminium ion analogue. Therefore it was not as energetically favourable to ring-open (Scheme 3.22).

Scheme 3.22: When the fullerényldihydropyrrole 148 was exposed to the reductive ring-opening conditions, it did not ring-open but was reduced stereoselectively to provide the cis-fulleropyrrolidine 121.

The proposed mechanism for the ring-opening of the methanofullerene 147 to form the dihydrofullerencyl derivative 161 has been previously reported by our group, albeit on the incorrect diphenylimino methanofullerene derivative, and is expected to proceed via complexation of BF₃ with the imino nitrogen which activates the imino carbon rendering it susceptible to hydride attack (Scheme 3.23). This results in migration of the imine double bond and formation of the fullerényl carbanion. The driving force for such a ring-opening must be the stabilisation of the fullerényl carbanion by delocalisation over the electron deficient fullerene cage and the loss of the ring-strain upon ring-opening of the cyclopropane ring. The imine bond of the fullerényl anion A (Scheme 3.23) was then
reduced forming intermediate B. The free anion B can then eliminate the addend to form pristine fullerene and eventually 163. Alternatively, B can be protonated upon aqueous work-up to form the observed ring-opened product 161.

Scheme 3.23: Proposed mechanism for the reductive ring-opening of methanofullerene 147.

Notably, efforts to hydrolyse the imine group of the methanofullerene 147 under acidic conditions (32% HCl, 0.5 mL) in THF at RT for 16 h produced a highly polar
insoluble material that could not be characterised or successfully derivatised to aid identification.

### 3.9 Manganese(III) mediated radical additions to fullerene

Manganese(III) acetate has been shown to readily abstract a hydrogen atom from activated methylene compounds with the corresponding carbon centered radical then adding to alkenes and alkynes.\(^\text{151}\) Manganese(III) acetate mediated radical additions to fullerene has recently been reported with the synthesis of 1,4-dihydro[60]fullerenyl adducts (164) derived from methyl and ethyl malonates, and a methano[60]fullerenyl derivative (165) was generated from malonitrile (Scheme 3.24).\(^\text{152, 153}\) This prompted our interest in applying manganese induced radical additions of iminoglycinate derivatives to [60]fullerene to synthesise protected fullerenyl amino acids and investigate the contributing factors to the product outcomes.

![Scheme 3.24](image)

\(a\) - Mn(III)(OAc)_2.2H_2O, 160 °C, chlorobenzene, 1 h

**Scheme 3.24:** Mn(III) mediated radical addition of activated methylene compounds to fullerene.
3.9.1 Addition of alkyliminoglycinates (138-140) to \( \text{C}_6\text{O}_6 \) under Mn(III) induced radical conditions

In a typical reaction, a solution of ethyl \( N\)-\((2,2\text{-dimethylpropylidene})\)glycinate (138) and \( \text{C}_6\text{O}_6 \) in chlorobenzene was treated with mangense(III) acetate dihydrate (2 equiv.) and the reaction mixture was heated at reflux for 1 h. The solvent was removed \textit{in vacuo} and the crude product was subjected to silica gel chromatography providing the known fulleropyrrolidine 121 in 38% yield, as a 5 : 1 mixture of \textit{cis} to \textit{trans} stereoisomers (Scheme 3.25). The mechanism of addition was expected to proceed through the addition of the \( \alpha \)-centered radical of 138 (138\*) to \( \text{C}_6\text{O}_6 \) to generate the intermediate radical 121A. The fullerene radical then attacked the imine to form the pyrrolidine radical 121B, which overcame the steric hinderance of the tert-butyl group and abstracted a H-atom from 138 to generate 121 and 138*.

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{H} \quad \text{OEt} \\
\text{OEt} &\quad \text{H}_2\text{N} \quad \text{OEt}
\end{align*}
\]

\[
\text{H} \quad \text{N} \quad \text{OEt} \\
\text{OEt} &\quad \text{H} \quad \text{N} \quad \text{OEt}
\]

\[
\begin{align*}
\text{Mn(III)} &\quad \text{Mn(II)} \\
\text{H}_2\text{N} &\quad \text{H} \quad \text{OEt} \\
\text{OEt} &\quad \text{H}_2\text{N} \quad \text{OEt}
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{O}_6 &\quad \text{H}_2\text{N} \quad \text{OEt} \\
\text{OEt} &\quad \text{H}_2\text{N} \quad \text{OEt}
\end{align*}
\]

Scheme 3.25: Synthesis of 121 through Mn(III) mediated radical addition of 138 to fullerene.
When ethyl diphenyliminoglycinate (96a) was treated with [60]fullerene under identical conditions the well-known fullerenyldihydropyrrole 106a was isolated in 25% yield (Scheme 3.26). As with the radical formation of 121, a pyrrolidine radical intermediate 166 was speculated to form. However this radical is more sterically hindered than 121B and it was assumed that it underwent other processes before H-atom abstraction of 96a could occur. Additionally it was speculated that if sufficient quantities of Mn(III) were present the intermediate 166 could form the Mn-enolate 167, which could then provide the cyclopropyl adduct 97a. Despite increasing the Mn(III) to 10 equiv. none of this adduct was observed, and could be attributed to either the rate of formation of 168 (intramolecular) over the enolisation of 166, or the formation of the less strained 106a compared to 97a. Another plausible mechanisms for the formation of 106a, involves the complexation of 168 with Mn(III) to form 169 which could then lose a proton and Mn(II) to form 106a. Alternatively 168 could coordinate with another equivalent of Mn(III) to form the Mn(III)-enolate 170 which could then collapse to form Mn(II) and 106a (Scheme 3.26).
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

![Chemical structures and reactions]

Mn(III),(OAc)₃,2H₂O, 160 °C, chlorobenzene, 1 h, 25%

Scheme 3.26: Plausible mechanistic pathways for the generation of 106a from the radical addition of 96a to fullerene.

Notably, attempts to add the imine 139 to [60]fullerene via a Mn(III) mediated radical addition were unsuccessful with pristine fullerene returned and imine degradation indicated by TLC analysis of the crude reaction mixture. Likewise the camphor iminoglycinate 140b did not add to C₆₀ under these conditions.
3.9.2 Manganese(III) mediated addition of thioiminoglycinates (143-144) to C\textsubscript{60}

A solution of the thioimine 143 (2 equiv.) and [60]fullerene (1 equiv.) in chlorobenzene was treated with manganese(III) acetate (2 equiv.) and the suspension was heated at reflux for 2 h. The cooled solution was added directly to a flash silica gel column and elution with CH\textsubscript{2}Cl\textsubscript{2}/hexanes (7 : 3) provided the thiomethylfullerenyldihydropyrrole 171 in 35% yield (Scheme 3.27). Confirmation of the structure was provided by analysis of its \textsuperscript{1}H NMR spectrum, which indicated retention of the ethyl ester resonances that had a complex splitting pattern indicative of their close proximity to the newly formed stereogenic centre. Important in the determination of the structure of 171 was the relative integration of the upfield singlet resonance at 2.96 ppm with a relative integration of 3H, which indicated the loss of one S-methyl group. Examination of the \textsuperscript{13}C NMR spectrum detailed the lack of a plane of symmetry with 50 fullereryl sp\textsuperscript{2} resonances observed. Two downfield signals at 175.2 and 170.1 ppm corresponded to the imine carbon and the carbonyl of the ester, respectively. Analysis of the ESI mass spectrum showed a peak at m/z 879 and was assigned as the molecular ion. Recently, work has been published by another group on the synthesis of this compound, however they accessed this molecule through a 1,3-dipolar addition reaction in an optimised yield of 9%. Importantly, the published spectral data is in agreement with this analysis.\textsuperscript{154}
Scheme 3.27: Proposed mechanism of addition of iminoglycinate 143 to fullerene providing the fullerenyldihydropyrrole 171.

Unfortunately when the dithiocyclohexyliminoglycinate 144 was exposed to the temperature required for the reaction to take place it decomposed before any significant formation of a fullerenylderivative occurred.

3.9.3 Manganese(III) mediated radical addition of ethyl benzylidenediglycinate to C$_{60}$

A solution of the imine 146 (2 equiv.) and C$_{60}$ (1 equiv.) in chlorobenzene was treated with manganese(III) acetate (2 equiv.) and the reaction mixture was heated at reflux for 1 h providing the fulleropyrrolidine 155 in 41% yield as a 2 : 1 mixture of cis and trans isomers, respectively (Scheme 3.28). To ensure this was not a thermal addition like that already reported,$^{150}$ the reaction was repeated in the absence of manganese(III) acetate providing the same fulleropyrrolidine 155 but in a substantially lower yield of 8% (2 : 1 mixture of cis and trans isomers). This supported the notion that the manganese was playing a key role, most likely as a radical initiator, to generate the corresponding fullerenyldadduct.
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

**Scheme 3.28:** Synthesis of 155.

3.10 Further investigation into the manganese(III) mediated radical addition of N-protected amino acids to fullerene

Before continuing the effort to obtain a cyclopropylfullerenyl amino acid, the manganese(III) acetate mediated radical addition of various iminoalaninate derivatives was examined. To this end *tert*-butyl-N-(2,2-dimethylpropylidene)alaninate 172 (Scheme 3.29)\(^{143}\) was synthesised under standard imine formation conditions.

**Scheme 3.29:** Synthesis of 173.

The imine 172 was treated with fullerene under the previously reported conditions (Section 3.9.1) affording the corresponding fulleropyrrolidine 173 as a predominately one isomer (only traces of the other isomer present). As expected, the yield was low compared to the glycinate derivatives which was attributed to both the relative difficulty in forming a
tertiary radical and the steric considerations of bond formation. Attempts to enhance the yield by increasing the reaction time (2 h to 8 h) resulted in a marginal increase in yield, from a trace amount to 6%.

Evidence for the proposed structure of 173 was provided by analysis of the $^1$H NMR spectrum, which showed two 9H singlets at 1.49 and 1.55 ppm assigned as the tert-butyl resonances. The shift downfield of the 3H singlet, assigned as the methyl group from the alanine moiety, from 1.29 ppm in 172 to 2.31 ppm in 173, was expected due to its close proximity to the fullerene cage. The loss of the 1H quartet at 3.69 ppm assigned as the methine proton in 172 also supports addition to C$_{60}$. The two 1H doublets at 4.36 and 4.72 ppm (both $J = 15.2$ Hz) were assigned as the NH and CH of the pyrrolidine ring, respectively. The geometry of the predominant isomer could not be determined with the limited spectral data. Further support of the structure was provided by ESI-MS analysis, which showed a peak at $m/z$ 933 and was assigned as the molecular ion.

Low yields and the relative instability of the product meant $^{13}$C NMR and 2D NMR experiments were not acquired so this structure can only be tentatively assigned. However, the trends observed in other similar compounds as well as the $^1$H NMR and ESI-MS data of 173 are consistent with the proposed structure.

Notably, efforts to add the more sterically hindered diphenyliminoalaninate 174 to [60]fullerene were unsuccessful with only traces of an insoluble material formed despite using extended reaction times (Scheme 3.30).
Chapter 3: Synthesis and Addition of N-protected Amino Acids to Fullerene

3.11 Summary/conclusions

The manganese(III) mediated addition of iminoglycinates to [60]fullerene failed to generate the corresponding methanofullereryl derivatives but rather provided a new method for the generation of fulleropyrrolidines 121, 147, 155 and 173 and fullerenyldihydropyrroles 106a and 171. The procedure itself was not always effective in delivering fullerenyl adducts, which was speculated to be a result of addend instability at the required high reaction temperatures.

3.12 Alternative N-protected amino ester for Bingel cyclopropanation addition to fullerene

The use of phthalic anhydride to protect the amine group of amino acids is well established. The phthalate group maintains the activation of the methylene carbon, albeit not as much as the analogous imine, making a Bingel addition reaction to fullerene a likely proposition.
3.12.1 Synthesis and bromination of phthalimides

Ethyl glycinate hydrochloride (1.1 equiv.) was suspended in toluene and treated with Et₃N (2 equiv.) and phthalic anhydride (1 equiv.). The reaction was heated at reflux under azeotropic conditions providing the known phthalimide 175 in 93% yield (Scheme 3.31).

A solution of the phthalimide 175 (1.2 equiv.), CBr₄ (1.2 equiv.) and fullerene (1 equiv.) was treated with DBU (3.5 equiv.) at RT (Scheme 3.23). After 24 h TLC analysis of the reaction mixture indicated the presence of only starting materials. The reaction temperature was then increased from RT to 50 °C and the mixture was left for another 12 h. Unfortunately after this period of time only starting material was present (TLC analysis). Notably, efforts to add 175 to fullerene via a manganese(III) mediated radical addition were also unsuccessful with both starting materials returned. Increasing reaction time resulted in the formation of baseline polymeric material as judged by TLC analysis.

Scheme 3.31: Attempts to add phthalimide 175 to fullerene were unsuccessful.

The lack of success in generating a fullereryl adduct from the Bingel cyclopropanation reaction of 175 with C₆₀ was expected to be due to little or no bromination of 175. Therefore, attempts to first brominate the phthalimide 175 were undertaken. Despite using high temperatures and large excesses of halogenating agents (Br₂, CBr₄) and bases (KHMDS, DBU), isolation of the desired α-bromo derivatives was
not possible. A method for the addition of a bromine group to the \(\alpha\)-position of the analogous methyl ester of phthalimide 175 has been reported.\textsuperscript{157} In spite of the long reaction time and poor yield, the lack of success encountered trying to develop alternative methods prompted us to reconsider this method.

Thus the ethyl ester 175 was photolysed with NBS for 3 h in carbon tetrachloride providing the undesired bromoester derivative 176 and traces of 177 (Scheme 3.32). This was a result of radical hydrogen abstraction and bromination of the CH\(_2\) of the ethyl ester rather than the bromination of the activated methylene carbon. Confirmation of the structure of 176 was provided by analysis of its \(^1\)H NMR spectrum, which showed a downfield quartet at 6.68 ppm with a relative integration of 1H, assigned as H\(_a\) (Scheme 3.24). Further upfield at 4.46 ppm an AB quartet \((J = 17.7\) Hz) with a relative integration of 2H was present and assigned as the activated methylene protons with the splitting pattern due to their close proximity to the newly formed stereogenic centre. While in the \(^{13}\)C NMR spectrum of 176 the emergence of a resonance at 71.7 ppm was assigned as the C\(_a\) carbon. Confirmation of the structure was provided by analysis of the ESI mass spectrum, which showed peaks at \(m/z\) 313 \((^{79}\)Br), and 315 \((^{81}\)Br) with an isotopic pattern indicative of the presence of a bromine atom.

![Scheme 3.32: The bromination of the phthalimide 175.](image_url)
Since the radical bromination occurred at the CH$_2$ of the ethyl ester and only traces of the useful dibromoderivative 177 were isolated, the phthalimide methyl ester 178 was synthesised under identical conditions to that reported for the synthesis 175 providing the analogous phthalimide 178 in good yield (91%). Using the modified literature method, a suspension of the phthalimide 178 in carbon tetrachloride was treated with NBS (2 equiv.) under irradiation with a UV lamp for 10 h, before being stirred for 10 h at RT. This was followed by the addition of NBS (2 equiv.) then the suspension was irradiated for a further 10 h. Purification by silica gel column chromatography provided the desired α-bromophthylglycinate 179 in 21% yield (Scheme 3.33), which was spectroscopically identical to that reported in the literature. The decrease in stability and ease of formation of α-carbon-centered radicals in N-phthaloyl protected amino acids is known, and is the reason for this poor yield.

Scheme 3.33: Synthetic plan to incorporate fullerene into peptides.
3.12.2 Bingel cyclopropanation of [60]fullerene with 179

A solution of the α-bromophthylglycinate 179 (1.2 equiv.) and [60]fullerene (1 equiv.) in toluene was treated with DBU (3.5 equiv.) at RT for 16 h. The reaction mixture was then concentrated under reduced pressure and then subjected to silica gel column chromatography, to provide the methanofullerene 180 in 37% yield (Scheme 3.33). Analysis of the $^1$H NMR spectrum of 180, indicated the loss of the resonance attributed to the α-hydrogen (6.86 ppm) and a significant downfield shift of the ortho-phthyl protons from 7.87 to 8.03 ppm caused by the relatively close proximity to the fullerene cage. Upfield the presence of a strong singlet at 4.01 ppm, with a relative integration of 3H, was assigned as the methyl group of the ester. Examination of the $^{13}$C NMR spectrum showed the fullerenyl sp$^2$ carbon chemical shift region to be highly crowded (141-146 ppm), compared to that of fullerenyldihydropyrroles (typically 135-153 ppm). A plane of symmetry, which bisects the fullerenyl sp$^3$ carbons was evident by the presence of a single sharp resonance at 70.9 ppm assigned to the two equivalent fullerenyl sp$^3$ carbons. This plane of symmetry was further confirmed by the presence of 28 full-intensity and four half-intensity fullerenyl sp$^2$ resonances (Figure 3.8). Unfortunately the distance from any protons to the carbon-bridge and fullerenyl sp$^3$’s eliminated the possibility of meaningful long-range $^1$H-$^{13}$C correlations in the HMBC experiments. However the possibility of any other sized ring, including a five-membered ring, was eliminated by the symmetry inferred by the $^{13}$C NMR spectrum. Further confirmation of the structure of 180 was provided by analysis of its ESI-MS spectrum, which displayed a peak at $m/z$ 938 assigned as the molecular ion.
It is important to note that the slow addition of DBU (over 30 min) to the solution was crucial in maximising the conversion to methanofullerene 180. This has found to be the case in other related systems as well.\textsuperscript{159} It should also be highlighted that excluding the relatively unstable methanofullerene 147, this represents the first reported synthesis of a stable protected $\alpha$-substituted methanofullerenyl amino acid.

![13C NMR spectrum](image)

**Figure 3.8**: $^{13}$C NMR spectrum (150 MHz, CDCl$_3$/CS$_2$; (2 : 3)) of fullerenyl sp$^2$ chemical shift region of compound 180. X denotes half-intensity peaks.

### 3.12.3 Future directions

Deprotection of the carboxyl group of 180 should be readily achieved using the established Lewis acid (BBr$_3$) method (Scheme 3.33, Section 2.4). Carboxyl coupling should also be forthcoming, again, using the established methodology (EDCI/HOBt). Amine deprotection is anticipated to be less straightforward with typical conditions for phthyl-removal requiring primary or secondary amine bases, which may attack the electron-deficient fullerencyl cage.\textsuperscript{54} However within the literature there exist methods for the removal of phthyl-derived groups from primary amines, which could be slightly modified...
to be compatible with fullerene thus potentially providing access to $\alpha$-fullerenyl glycinate esters. The most promising uses a tetrachlorophthyl unit as an amine protecting group, which can be removed under reductive conditions (NaBH$_4$) in the presence of AcOH.$^{146}$ It is hoped replacement of the sodium borohydride, which could potentially reduce the fullerene cage, with the weaker reducing agents such as sodium cyanoborohydride, will still allow for amine deprotection. It is then anticipated that amine coupling could then occur under the same conditions established in the dihydro case (Section 2.3.3 – 2.3.5).

### 3.13 Conclusions

The fulleropyrrolidines 121 and 155 were synthesised using base-assisted cycloaddition reactions representing a mild and potentially general method for the synthesis of fulleropyrrolidines, which are typically formed under relatively harsh conditions (see Chapter 1, p.16). Despite finding that all the iminoglycinates examined were unsuitable precursors for the generation of stable methanofullerenyl derivatives the reductive ring-opening reaction was utilised to open the cyclopropyl ring of the relatively unstable compound 147 to deliver the more stable 1,9-dihydrofullerene 161. Additionally a method for the reduction of non-conjugated dihydropyrroles (*e.g.* 148) to generate fulleropyrrolidines was also discovered. Importantly, a promising alternative route to gain access to protected methanofullerenyl amino acids was developed using $\alpha$-bromophthylglycinate, it is anticipated that this protected fullerenyl amino acid will be deprotected and coupled to peptides in the future.
4.1 Multifunctionalised [60]fullerene derivatives

Since the addition of the diphenyliminoglycinates 96 to [60]fullerene under Bingel reaction conditions provides the analogous fullerényldihydropyrrole and not the previously reported methanofullerene (Scheme 4.1), the reaction outcome for the addition of tethered iminoglycinates to [60]fullerene under Bingel reaction conditions was re-examined. The synthesis of alternatively multi-functionalised fullerene derivatives was also examined. However, before this can be discussed some terminology needs to be defined.

Scheme 4.1: The addition of diphenyliminoglycinates 96 to fullerene under Bingel reaction conditions provided the diphenylidihydropyrroles 106.

4.2 Bis-substituted [60]fullerene derivatives

[60]Fullerene contains 30 identical double bonds located at the 6,6-ring junctions, hence successive addition of independent addends to 
C<sub>60</sub> almost always results in a complex mixture of regio- and/or stereo-isomers (Figure 4.1). The cis-3, trans-2 and trans-3 bis-addition patterns are inherently chiral, meaning that bis-substitutions in these relative positions gives rise to chiral fullerényl adducts, regardless of whether the addends are identical, achiral or chiral. For example, the cis-3 tetraethyl ester 181 exists as both the optically active <sup>4</sup>C and <sup>4</sup>A enantiomers (Scheme 4.2). The term noninherently chiral refers
to the bis-addition patterns *cis*-1, *cis*-2, and *trans*-4 which are only chiral when substituted with two different addends.

**Scheme 4.2:** Two enantiomers of the $C_2$-symmetrical bis-adduct 181. The bis-adduct 181 can exist as clockwise (′C) or anticlockwise (′A) enantiomers.

### 4.2.1 Regioisomerism

In the addition of two different addends to $C_{60}$ (*i.e.* a bis-adduct) nine possible attachment sites exist, assuming that addition occurs across a 6,6-ring junction. If the second attachment is on the same hemisphere as the first, it is assigned *cis* regiochemistry, with *cis*-1 being closest to the first site of substitution followed by *cis*-2 then *cis*-3 (Figure 4.1A). The two substitution sites located on the equatorial belt are termed $e$-edge and $e$-face. Addition of the second attachment to the opposite hemisphere results in *trans* regiochemistry with the *trans*-4 position being closest to the equator followed by *trans*-3 then *trans*-2 and finally *trans*-1.

As an example, the addition of the nitrene precursor 182 to the well-studied methano[60]fullerene 70 leads to a mixture of all nine possible regioisomers (Figure 4.1B). Figure 4.1C shows the relative abundance of each regioisomer. The common feature of this and other studies of independent bis-additions to [60]fullerene is that the differences in the calculated relative heats of formation between regioisomers are not high enough to impose significant regioselectively.
4.2.2 Controlling regiochemical outcome

One way to overcome the lack of selectivity experienced with the addition of independent addends to C_{60} is through the use of a tether, which attaches reactive groups together through a typically rigid linker molecule (see Chapter 1, Section 1.6).\textsuperscript{124} This strategy was utilised during our previous studies towards the synthesis of multifunctionalised fullerenyl amino acids.\textsuperscript{108, 109}
4.3 Structural reassignment of tethered diphenylimino bis-additions to [60]fullerene

In light of the structural reassignment for the addition products of diphenyliminoglycinates to [60]fullerene under Bingel reaction conditions (Chapter 2, Section 2.1), the products from the addition of bis-diphenyliminoglycinates to fullerene also required re-examination. Therefore, as previously reported, the meta-tethered and para-tethered bis-iminoglycinates, 183 and 184, respectively were synthesised in three steps from benzenedimethanol (Scheme 4.3).

![Scheme 4.3: Synthesis of tethered bis-iminoglycinates 183 and 184.](image)

The addition of the bis-diphenyliminoglycinates 183 and 184 to [60]fullerene under Bingel reaction conditions were originally reported to furnish the corresponding bis-methano[60]fullerene derivatives. Therefore, the bis-substituted [60]fullerene analogues 189-192 were re-synthesised and their 1D and 2D NMR spectra analysed (Scheme 4.4).
Chapter 4: Multifunctionalised Fullereryl Derivatives

The regiochemical outcomes from bis-additions to the [60]fullerene cage remain as previously reported, with symmetry arguments and UV-vis spectral data from all the bis-substituted analogues (189-192, Scheme 4.4) providing evidence for the regiochemical outcome with analysis of their 2D-INADEQUATE spectra unambiguously confirming their regiochemistries. The symmetry of the bis-substituted fullereryl adducts are equivalent regardless of whether or not the attachments are via three- or five-membered rings, therefore analysis of the $^{13}$C NMR spectra could not differentiate between the two possible structures. However, re-examination of the HMBC correlations showed that all bis-substituted fullereryl adducts were the corresponding bis-[60]fullerenylidihydropyrroles (189-192) and not the previously reported bis-methano[60]fullerenes. The key to determining this was the observation of a strong 3-bond correlation from $H_{\alpha}$ to $C_{\beta}$, and the absence of a correlation from $H_{\alpha}$ to any downfield resonance attributable to an imine moiety (Scheme 4.4, Table 4.1). Table 4.1 summaries the HMBC correlations observed for each bis-adduct previously reported with the re-assigned structures shown in Scheme 4.4.
Scheme 4.4: Addition of bis-iminoglycinates to fullerene under Bingel reaction conditions provided the analogous bis-fullerényldihydropyrroles 189-192 and not the previously reported bis-methanofullerenes.

Table 4.1: HMBC correlations

<table>
<thead>
<tr>
<th>Compound</th>
<th>H_α (ppm)</th>
<th>C_β (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>189</td>
<td>8.04, 7.92</td>
<td>97.06</td>
</tr>
<tr>
<td>190</td>
<td>8.21, 8.17</td>
<td>96.02</td>
</tr>
<tr>
<td>191</td>
<td>8.25, 8.09*</td>
<td>95.94*</td>
</tr>
<tr>
<td>192</td>
<td>8.02, 7.92</td>
<td>96.74</td>
</tr>
</tbody>
</table>

* Due to the poor solubility of this compound in organic solvents it was trans-esterified to the corresponding ethyl ester to facilitate spectral acquisition. NB the ortho protons of the phenyl rings are not equivalent, as the symmetry plane does not bisect C_β.

These new structural assignments help explain the difference in regiochemical outcomes between tethered bis-malonate esters\textsuperscript{160} and the bis-N-(diphenylmethylene)glycinate esters, derived from meta- and para-benzenedimethanol scaffolds, with [60]fullerene under Bingel reaction conditions (Chapter 1, Section 1.6). These differences in regiochemistry can now be understood in terms of their different reaction mechanisms.
4.3.1 Changing the regioisomeric ratio for the addition of tethered diphenylimino bis-addends to [60]fullerene

In order to investigate factors controlling the regioselectivity of the addition of the meta- and para-tethered bis-iminoglycinates to C\textsubscript{60} (Scheme 4.4), the reaction solvent and the [60]fullerene concentration were varied. The product yields and regioselectivities are tabulated below (Table 4.2 and 4.3). The other reagents involved in the Bingel reactions were kept constant, DBU (4 equiv.) and CBr\textsubscript{4} (2.5 equiv.) and all reactions were performed at RT for 3 h. The crude reaction mixture was then subjected to flash silica gel chromatography and the compounds 189 and 190 (from 183) were collected together to determine regioisomeric ratio (from \textsuperscript{1}H NMR analysis, Table 4.2). Likewise compounds 191 and 192 were collected as a mixture and analysed by \textsuperscript{1}H NMR (Table 4.3), and all yields were determined by the combined yield of regioisomers.

Table 4.2: Regiochemical outcome for the addition of the meta-tether 183 to C\textsubscript{60} under Bingel reaction conditions at various reaction concentrations.

<table>
<thead>
<tr>
<th>#</th>
<th>Solvent (200 mL)</th>
<th>C\textsubscript{60} (mM)</th>
<th>Regiochemical outcome (189:190)\textsuperscript{a}</th>
<th>Yield mg. (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>7.6</td>
<td>2.8 : 1</td>
<td>48, (24%)</td>
</tr>
<tr>
<td>2</td>
<td>Chlorobenzene</td>
<td>7.6</td>
<td>2.0 : 1</td>
<td>45, (23%)</td>
</tr>
<tr>
<td>3</td>
<td>o-Dichlorobenzene</td>
<td>7.6</td>
<td>1.9 : 1</td>
<td>43, (22%)</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>15</td>
<td>3.0 : 1</td>
<td>98, (25%)</td>
</tr>
<tr>
<td>5</td>
<td>Chlorobenzene</td>
<td>15</td>
<td>2.1 : 1</td>
<td>101, (26%)</td>
</tr>
<tr>
<td>6</td>
<td>o-Dichlorobenzene</td>
<td>15</td>
<td>1.8 : 1</td>
<td>96, (24%)</td>
</tr>
<tr>
<td>7</td>
<td>Chlorobenzene</td>
<td>30</td>
<td>1.9 : 1</td>
<td>214, (28%)</td>
</tr>
<tr>
<td>8</td>
<td>o-Dichlorobenzene</td>
<td>30</td>
<td>2.0 : 1</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by \textsuperscript{1}H NMR analysis of a mixture of 189 and 190. \textsuperscript{b} Yield refers to combined yield of 189 and 190. \textsuperscript{c} This reaction was monitored via \textsuperscript{1}H NMR every 30 min; regiochemical ratios remained constant throughout.
Table 4.3: Regiochemical outcome for the addition of the para-tether 184 to C₆₀ under Bingel reaction conditions at various reaction concentrations.

<table>
<thead>
<tr>
<th>#</th>
<th>Solvent (200 mL)</th>
<th>C₆₀ (mM)</th>
<th>Regiochemical outcome (191:192)</th>
<th>Yield mg. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>7.6</td>
<td>3.3 : 1</td>
<td>57, (29%)</td>
</tr>
<tr>
<td>2</td>
<td>Chlorobenzene</td>
<td>7.6</td>
<td>2.4 : 1</td>
<td>51, (26%)</td>
</tr>
<tr>
<td>3</td>
<td>o-Dichlorobenzene</td>
<td>7.6</td>
<td>2.9 : 1</td>
<td>53, (27%)</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>15</td>
<td>3.5 : 1</td>
<td>119, (30%)</td>
</tr>
<tr>
<td>5</td>
<td>Chlorobenzene</td>
<td>15</td>
<td>2.3 : 1</td>
<td>104, (26%)</td>
</tr>
<tr>
<td>6</td>
<td>o-Dichlorobenzene</td>
<td>15</td>
<td>3.2 : 1</td>
<td>110, (28%)</td>
</tr>
<tr>
<td>7</td>
<td>Chlorobenzene</td>
<td>30</td>
<td>2.6 : 1</td>
<td>207, (27%)</td>
</tr>
<tr>
<td>8</td>
<td>o-Dichlorobenzene</td>
<td>30</td>
<td>3.1 : 1</td>
<td>234, (30%)</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR analysis of a mixture of 191 and 192. b Yield refers to combined yield of 191 and 192.

Through systematic variation of the solvent and reaction concentration it was observed that solvent choice significantly influenced the regiochemical outcome. Toluene was found to be the best solvent for increasing the relative proportion of the major isomer in both the meta- and para- dimethylbenzene scaffolds at all examined concentrations (Table 4.2 entries 1 and 4, Table 4.3 entries 1 and 4). Toluene however, did not readily dissolve all the [60]fullerene at 30 mM concentration. Reaction concentration was found to have less of an influence on the regiochemical outcome with only a slight change observed.

In addition, the Bingel reaction was monitored via ¹H NMR spectroscopy every 30 min over a period of 3 h with no change in the ratio of the regioisomeric products being observed over the course of the reaction. Examination of the regiochemical outcome when the reaction was conducted at 0 °C and 40 °C also revealed no significant change in the regiochemical ratio, suggesting that these reactions are under kinetic control.

4.3.2 Altering product outcome

On larger scale reactions (>1 g of [60]fullerene) the addition of the meta-tether 183 to C₆₀ under the optimised Bingel reaction conditions provided the expected bis-adducts
(189-190, in a 2:1 ratio, respectively) along with alcohol 193 (Scheme 4.5). Proof of the structure of 193 was provided by analysis of its $^1$H NMR spectrum, which detailed two singlets at 5.52 and 4.63 ppm, each with a relative integration of 2H, assigned as the benzylic protons. Examination of the $^{13}$C NMR spectrum of 193 revealed two upfield resonances at 68.1 and 64.8 ppm, which were assigned as the benzylic carbons. The presence of a broad resonance at 82.7 ppm was characteristic of the fullerenyl sp$^3$ resonance of a fullerenyldihydropyrrole, this was confirmed by the presence of a peak at 95.9 ppm, indicative of the dihydropyrrole sp$^3$ carbon resonance in these structures. It was expected that two fullerenyl sp$^3$ resonances would be observed however due to their similar chemical enviroment a coincidental overlap occurred and it was not possible to resolve the peaks. The fullerenyl sp$^2$ region contained the expected 28 full-intensity resonance and 2 half-intensity resonances, with the diphenyls ipso carbon resonance appearing at 141.8 ppm. Confirmation of the structure of 193 was provided by analysis of its ESI-MS spectrum, with a peak at m/z 1077 corresponding to the molecular ion (M$^+$).


Scheme 4.5: Formation of 193 was expected to proceed via the addition of 194 to fullerene.

The fullerenyl alcohol 193 was thought to arise via the alcohol 194, which was probably obtained from saponification of the addend 183, due to the traces of water in the reaction mixture (Scheme 4.5). The alcohol 194 could then be brominated in situ and subsequently add to C\textsubscript{60} in a typical addition/elimination reaction. The source of water for the hydrolysis was most likely from a trace impurity in the solvent. It is unlikely that ester hydrolysis occurred after the first addition of the addend to the cage, as the rate of the intramolecular reaction forming the fullerenyl bis-adducts 189-190 would be expected to be considerably faster. Notably, the presence of a fullerenyl bis-adduct without a tether was not observed, likewise the corresponding mono-carboxylic acid 114 was not isolated (Scheme 4.5).

Optimisation of the yield of the alcohol 193, over the bis-adducts 189 and 190 indicated that the amount of alcohol 193 produced was proportional to the amount and rate of addition of base (DBU) and the water content of the solvent. Therefore a solution
containing the addend 183 (1.4 equiv.), CBr₄ (2.4 equiv.) and [60]fullerene (1 equiv.) in AR grade o-dichlorobenzene (not distilled) was treated with DBU (10 equiv.) over 10 seconds. After flash silica gel column chromatography the fullerene alcohol 193 was isolated in 20% yield. Although 193 was not used further in this study it could be a useful precursor for the synthesis of higher ordered structures such as tris-adducts, as shown in Scheme 4.6.

![Scheme 4.6: Compound 193 could be used as a precursor in the synthesis of tris-adducts.](image)

4.4 Towards multifunctionalised fullerene derivatives

Previous work in our laboratory described the generation of the dihydrofullerenyl derivative 195 when the bis-diphenylfullerenyldihydropyrrole 189 was subjected to reductive ring-opening reaction conditions, rather than the desired bis-dihydrofullerenyl derivative 196 (Scheme 4.7). The key intermediate 196 could in principal be used to access bis-fullerenyl N-peptides of the general structure 197 utilising the chemistry established for the analogous mono-adducts (Sections 2.3.3 and 2.3.4). Therefore work was conducted towards the synthesis of 196.
Chapter 4: Multifunctionalised Fullerenyl Derivatives

Scheme 4.7: Bis-ring-opening of 189 would produce 196, which contains two new stereogenic centres, denoted by *.

4.4.1 Reductive ring-opening of fullerenyldis-adducts

The extension of the optimised conditions developed for the reductive ring-opening of the monoadduct 106a (Chapter 2, Section 2.2.1) to the bis-adduct 189 did not represent an efficient method for the generation of the analogous bis-ring-opened product 196, but rather lead to the isolation of the dihydrofullerenyl derivative 195 in 68% yield, reduced addend 198 (8%) and C₆₀ (Scheme 4.7). Notably, traces of what was speculated to be the bis-dihydrofullerenyl derivatives (196) were evident from TLC analysis of the reaction mixture. It was observed (via TLC analysis) that ring-opening of the bis-fullerenylidihydropyrrole 189 produced two products, speculated to be the racemate (R,R and S,S) and the meso compounds (R,S)/(S,R) 196.

In order to identified these two products an optimisation study was conducted for the conversion of the dihydropyrrole 189 to the bis-dihydrofullerenyl derivatives 196 as
shown in Table 4.4. Variation in the stoichiometry of reagents and reaction conditions (time and temperature) yielded the optimal conditions for the generation of the bis-dihydrofullerenyl derivatives. That is, a solution of 189 in THF at –78 °C was treated for 10 min with 10 equiv. of the Lewis acid to form the boron-complex. This was followed by the addition of the reducing agent (10 equiv.) and glacial acetic acid (0.1 mL), whose speed of addition had no noticeable effect on product outcome. Under these conditions analysis of the crude reaction mixture by TLC indicated complete conversion of 189 to the bis-dihydro analog 196, in approximately 80% purity, with no traces of either 189 or the unwanted dihydrofullerenyl side product 195. It is critical to note that this optimisation study was conducted on a small scale (5 mg of 189) and the reaction outcome was determined by visual analysis of the reaction mixture by TLC.

Table 4.4: Optimisation of the bis-reductive ring-opening of 189.

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>BF$_3$.(OEt)$_2$ (equiv.)</th>
<th>NaCNBH$_3$ (equiv.)</th>
<th>AcOH (mL)</th>
<th>189 (%)</th>
<th>195 (%)</th>
<th>196 (%)</th>
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<td>70</td>
</tr>
</tbody>
</table>

* All reactions were performed with 189 concentrations at 0.5 mg/mL. * Reaction percentage conversions were determined by analysis of the TLC of the crude reaction mixtures.

Once the reaction conditions for the bis-reductive ring-opening of 189 to produce 196 were established the reaction was scaled-up to allow for complete characterisation of this key intermediate. Hence a solution of 189 and BF$_3$.(OEt)$_2$ at –78 °C was treated with NaCNBH$_3$ followed immediately by the addition of glacial acetic acid and the reaction...
mixture was then stirred for a further 15 min. Analysis of the crude mixture by TLC indicated almost complete conversion to the compounds of interest, speculated to be the rac- and meso- bis-dihydro derivatives 196 (Scheme 4.7). The remaining component of the reaction mixture appeared as unknown baseline material. The reaction mixture was then quenched with ice/water and the crude residue was then subjected to flash silica gel chromatography to deliver the racemic bis-dihydrofullerenyl derivative 196 \((S,S\) and \(R,R\)) in 8.5% yield. None of the meso form of 196 was isolated. Further elution provided the known dihydrofullerenyl derivative 195 (62%) and the reduced addend 198 (10%).

Analysis of the \(^1\text{H NMR}\) spectrum of 196 showed two strong singlets at 6.24 and 6.61 ppm, both with relative integrations of 1H, indicative of the fullerenyl protons (denoted by green circle, Figure 4.2). In conjunction with the gCOSY spectrum the four resonances corresponding to the diastereotopic benzylic protons were assigned as the four 1H doublets; \(J = 11.1\) Hz for the coupled resonances at 5.76 and 4.57 ppm and \(J = 11.7\) Hz, for the coupled resonances at 5.50 and 4.66 ppm. Confirmation of the structure of 196 was provided by analysis of the ESI mass spectrum, which showed a peak at \(m/z\) 1303 assigned as the molecular ion (M-H).

Interestingly, the meso compound was not isolated and was speculated to have decomposed during work-up. Since a symmetry plane would bisect the substitution sites of meso-196, the \(^1\text{H NMR}\) spectrum of this compound would be relatively simple compared to the rac-196, which does not possess any symmetry (Figure 4.2).
Chapter 4: Multifunctionalised Fullerene Derivatives

Figure 4.2: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of the bis-dihydrofullerene derivative rac-196, proton assignments were determined in conjunction with analysis of the gCOSY spectrum. X denotes CH$_2$Cl$_2$ resonance, the (R,R) enantiomer is inset.

Our analysis of the TLC of the crude reaction mixture before work-up indicated the presence of two products, speculated to be the racemate (S,S and R,R) and the meso- (R,S and S,R) bis-dihydrofullerene derivatives 196, and the absence of the dihydrofullerene derivative 195. Our results suggest that rac-196 is more stable than meso-196. However it appeared that 196 was unstable to the work-up and/or isolation processes and decomposed to form 195. Since the reduction was not conducted in a stereoselective fashion, and 189 does not possess any structural elements to direct hydride attack, it is reasonable to assume that both rac- and meso-196 would be formed. However, no structural proof for the existence of meso-196 has been found. In order to determine the cause of decomposition of 196 to 195, both the work-up and isolation procedures were systematically investigated.
Therefore, a reaction mixture, which contained mostly 196 (evident by analysis of the TLC), was poured into a separating funnel that contained CH$_2$Cl$_2$ and a saturated NH$_4$Cl solution. Immediately after this, TLC analysis of the organic layer indicated conversion of the majority of 196 to the analogous dihydroderivative 195. Once the solution of the crude material has been reduced in vacuo (at RT) and applied to a silica gel column the only products isolated were the mono derivative 195 (58%), pristine [60]fullerene (12%), and the reduced tether 198 (5%) (Scheme 4.7).

At this point it was still unclear as to why 196 was converting to 195. To examine this, the conversion of 189 to its analogous ring-opened products 196 was conducted again however, the step in the work-up procedure that involved washing the organic phase with NH$_4$Cl was omitted. Analysis of the reaction mixture by TLC indicated good conversion to the rac-196 and the product speculated to be the meso-196. Toluene was added and the THF removed in vacuo at RT, TLC analysis of the solution at this point indicated significant conversion to 195. Hexane was added to the solution and the precipitate was collected via filtration, then redissolved in CH$_2$Cl$_2$, TLC analysis indicated further degradation to the mono derivative 195. After column chromatography the only products recovered were C$_{60}$ (6%), 195 (55%), and the reduced addend 198 (11%).

The reaction was conducted again; TLC analysis indicated good conversion to the rac- and meso-196. At this point the reaction was quickly applied to a column containing a short plug of silica gel. Collection of the eluent and TLC analysis indicated the same decomposition products (195, 198 and C$_{60}$) with only traces of 196.

The necessity of the glacial acetic acid was examined next, hence the reaction was repeated in the absence of the protic acid and, as expected, did not proceed as smoothly as previously described, with more conversion to the mono derivative 195 indicated by
analysis of the reaction mixture prior to work-up (TLC). However there were still considerable amounts of 196 present. Application of this solution to a silica gel column and subsequent analysis by TLC of the eluent again indicated the dihydro derivative 195, C$_{60}$ and reduced addend 198. Following the above procedure but including a NH$_4$Cl wash had the same disappointing outcome.

It appeared that the main factor in the degradation process was temperature. This was demonstrated by allowing the reaction mixture, which contained mostly rac- and meso-196 (as judged by TLC analysis), to warm from –78 °C to RT. TLC analysis of the reaction mixture indicated the rapid conversion to the mono compound 195 almost immediately after removal from the –78 °C slush bath. Therefore, the procedures above were repeated and the temperature of the reaction mixture during work-up and isolation was kept as cold as possible (~0 °C) this appeared to slow the degradation process. However, only a few milligrams of the desired product rac-196 were isolated. Since this problem could not be readily overcome the reaction sequence to achieve 196 was not further pursued.

To see if the instability was conserved in the absence of the tether, 189 was transesterified to deliver the known diester 199 in 83% using a modified literature procedure (Scheme 4.8).\(^{108, 109}\) Interestingly the trans-4 diester 199 was found to be even more unstable to the reductive ring-opening conditions than the analogous tethered molecule 189, with complete conversion to the known dihydro derivative 99a, C$_{60}$ and the reduced addend 110 within minutes at 0 °C.
Chapter 4: Multifunctionalised Fullereryl Derivatives

Scheme 4.8: Reductive ring-opening of 199 provided 99a.

To study this reaction further the reductive ring-opening of the cis-3 regioisomer 190 was examined. Since the cis-3 bis-adducts are inherently chiral the starting diester 200 was a racemic mixture of both $^1A$ and $^1C$ enantiomers (Figure 4.3). Once ring-opening had been effected two additional racemic stereocentres would be formed giving rise to eight potential isomers.
Figure 4.3: Schlegel diagrams of the racemic *cis*-3 diester 200, which possess an axis of symmetry. The ester and diphenyl groups were removed for clarity.

Figure 4.4 illustrates two possible enantiomers, which could arise from the ring-opening of the racemic diester 200, which possess $C_2$ symmetry. Another pair of enantiomers of 201 exist with $C_2$ symmetry ($S,S$/$A$ and $R,R$/$C$), these being diastereomers of those shown in Figure 4.4. Since these compounds have an axis of rotation, the $^1H$ NMR spectrum would display a single set of resonances for the addends.
Figure 4.4: One set of enantiomers of 201 with $C_2$ symmetry, the diastereomic pair ($S,S^f/C$ and $R,R^f/C$) is not shown.

Figure 4.5 displays two enantiomers of 201, which do not possess any symmetry. Another analogous pair of enantiomers also exists ($S,R^f/A$ and $R,S^f/C$), these being diastereomers of those shown in Figure 4.5. Since these compounds do not have an axis of symmetry the $^1$H NMR spectrum would display a doubling-up of resonances for the addends.
To summarise, the cis-3 diester 200 exists as both the optically active $^fC$ and $^fA$ enantiomeric forms (Figure 4.3). Ring-opening of 200 would resulted in 201 with two additional stereocentres being formed giving rise to the possibility of four racemic diastereomeric products. Two of these diastereomers have an axis ($C_2$) of symmetry while the other two do not.

Thus a solution of the diester 200 in THF was subjected to the same reductive conditions developed for the ring-opening of the tethered trans-4 isomer 189. Analysis of the reaction mixture by TLC indicated complete consumption of the starting material. The crude residue was then subjected to column chromatography, and elution with $\text{CH}_2\text{Cl}_2$/hexanes (3 : 2) delivered two ring-opened isomers (201a and 201b), as a 1 : 1 mixture, and the known mono-adduct 99a, which co-eluted with the desired bis-adducts (Scheme 4.9).
**Scheme 4.9:** The ring-opening of 200 was expected to deliver various stereoisomers which would possess C₂ symmetry (201a) and no symmetry (201b).

Proof of the structure 201a and 201b was provided by analysis of the \(^1\text{H}\) NMR spectrum, which detailed three singlets at 6.505 (1H), 6.518 (1H) and 6.522 ppm (2H) indicative of the fullerenyl protons (Figure 4.6). This suggested that the mixture contained two diastereoisomers in a 1 : 1 ratio, one with C₂ symmetry (either a racemic mixture of (R, R, ′A) and (S, S, ′C) or a racemic mixture of (R, R, ′C) and (S, S, ′A)) and another without symmetry (either a racemic mixture of (R, S, ′A) and (S, R, ′C) or a racemic mixture of (R, S, ′C) and (S, R, ′A)). Further upfield at 4.59 ppm a 2H doublet (\(J = 12.5\) Hz) was found to couple to a broad 2H doublet (\(J = 12.0\) Hz) at 3.48 ppm. These peaks were assigned to the \(\text{H}_\text{C}\) and \(\text{NH}_\text{D}\) protons of the isomer possessing C₂ symmetry, that is, 201a (Figure 4.6).

The \(\text{CH}_\text{b}\) and \(\text{CH}_\text{b}′\) resonances for the isomers without an axis of symmetry (201b) appeared as two overlapping 1H doublets, (\(J = 12.0\) Hz) at 4.63 and 4.64 ppm. These resonances were found to couple to the 2H doublet of doublets (\(J = 12.0\) Hz, 3.0 Hz) at 3.28 ppm assigned as the two NH resonances (Figure 4.6). While a broad 4H singlet at 5.12 ppm was assigned as the \(\text{H}_\text{C}\) and \(\text{H}_\text{eC}′\) (coincident overlap). The lack of further spectroscopic data for 201a/b meant that they could only be tentatively assigned as the structures shown in Figures 4.4, 4.5 and 4.6. The observation of only two of the four possible diastereomic products suggests that the other isomers are less stable and are speculated to have degraded during work-up.
Chapter 4: Multifunctionalised Fullerenyl Derivatives

Figure 4.6: $^1$H NMR (500 MHz, CDCl$_3$) spectrum of the bis-dihydrofullerenyl derivatives 201a and 201b. X denotes a THF resonance, whilst O denotes resonances of the known dihydrofullerenyl derivative 99a.
Notably, when the tethered *cis*-3 isomer 190 was subjected to the same optimised reductive ring-opening conditions established for the *trans*-4 isomer, the product formed was found to be extremely unstable and rapidly converted to the monodihydrofullerenyl derivative 195 within minutes, with no evidence for the formation of the bis-dihydro derivative (Scheme 4.10).

![Scheme 4.10: Reductive ring-opening of 190 provided the dihydrofullerenyl derivative 195.](image)

4.4.1.1 Conclusions

Reductive bis-ring-opening of the tethered *trans*-4 isomer 189 provided the racemic bis-dihydro-derivative 196. When the *trans*-4 non-tethered diester 199 was exposed to the same conditions only the dihydrofullerenyl derivative 99a was isolated suggesting the tether played a role in stabilising the product (Schemes 4.7 and 4.8). Conversely when the tethered *cis*-3 analog 190 and the non-tethered diester 200 were exposed to reductive ring-opening conditions only the non-tethered derivative gave bis-dihydro-derivatives (201a/b Schemes 4.9 and 4.10). The exact reason for isolation of only some of the possible ring-opened isomers at this stage is unclear. Due to the general instability of the bis-dihydro compounds this line of synthesis was not further pursued. It should be noted however once isolated the bis-dihydro derivatives *rac*-196 and 201a/b were relative stable when stored in the freezer under an atmosphere of argon.
4.4.2 [60]Fullerenyl bis-peptides

Focus was then shifted to extending the carboxyl deprotection and coupling reactions, established on mono-adducts (Section 2.4), to bis-adducts (Scheme 4.11). Therefore, a solution of 189 in CH₂Cl₂ was treated with BBr₃ and stirred at RT for 15 h before being quenched with water. The product bis-acid 202 was then precipitated from a chloroform solution with hexanes as a brown solid in 58% yield. Interpretation of the ¹H NMR spectrum of 202 indicated the loss of the resonances attributed to the diastereotopic benzylic protons (5.06 and 5.71 ppm). In addition, the aromatic region of the spectrum contained less peaks, notably the loss of the upfield singlet (7.14 ppm) assigned as the proton attached to C2 of the aromatic ring of the tether. In addition, the emergence of a broad singlet at 8.71 ppm, with a relative integration of 2H, indicated the presence of the carboxylic acid protons. ESI-MS (-ve) analysis confirmed the structure with a peak at m/z 1193 assigned as the molecular ion (M-H)⁺. Notably the observation of the doubly charged anion at m/z 596, further supported the assignment, as the bis-acid would be expected to readily form a dianionic species (see Chapter 5 for further discussion on ESI-MS).

Scheme 4.11: Synthesis of the first reported fullerenyl bis-peptides.

To examine the scope of the coupling reaction established on the corresponding mono-substituted system, the bis-acid 202 was coupled with methyl L-phenylalaninate
using analogous reaction conditions to that described in Chapter 2, Section 2.4.2, however the reaction time was extended to 3 h to allow for the more sterically demanding addition of the second amino acid (Scheme 4.11). The reaction mixture was then applied directly to a silica gel column to deliver the fullerene bis-peptide 203 in 56% yield. Surprisingly, to the best of our knowledge, this is the first report of a fullerene bis-peptide.

Confirmation of the structure of the methyl ester 203 was provided by analysis of its $^1$H NMR spectrum, which revealed the loss of the broad singlet at 8.71 ppm corresponding to the carboxylic acid protons. The appearance of a broad 2H multiplet at 7.97 ppm was assigned to the amide protons of 203. Since the two addends coupled both had the L-configuration, there was no longer a plane of symmetry bisecting the substitution sites of the fullerene hence a doubling up of peaks was observed, as evident by the two strong 3H singlets at 3.73 and 3.75 ppm assigned as the methyl protons of the ester groups. In the $^{13}$C NMR spectrum of 203, 51 fullerene sp$^2$ resonances were observed indicating the absence of symmetry. Retention of the pyrrole rings was implied through the presence of resonances at 96.1 and 96.2 ppm, which are characteristic chemical shifts for the sp$^3$ carbons of diphenyldihydropyrroles, while two close peaks at 53.4 and 53.5 ppm where assigned to the carbon resonances of the methyl group of the esters. Finally ESI-MS spectral analysis supported the structural assignment with a peak at m/z 1518 assigned as the mono-sodiated molecular ion (M+Na)$^+$. 

Under identical conditions to that detailed above ethyl L-phenylalaninate was coupled to the bis-acid 202 furnishing the ethyl ester bis-peptide 204 in 58% yield.
4.4.2.1 Reductive ring-opening of bis-peptide 204

Due to the lack of success encountered in using standard reductive ring-opening conditions to affect ring-opening of the analogous monopeptide (Section 2.4.4), a protic acid catalysed reductive ring-opening of the bis-peptide 204 was attempted (Scheme 4.12). Hence a solution of 204 in THF was treated with glacial acetic acid and the solution allowed to stir at RT for 15 min before the addition of NaCNBH₃. The reaction mixture was stirred for a further 16 h then quenched with water to provide the known monopeptide 115 in 31% yield.

![Scheme 4.12](image)

**Scheme 4.12**: Under protic acid catalysed reductive ring-opening conditions the bis-peptide 204 was converted to the monopeptide 115.

While this was not the expected result it does hold some promise that with further development this method may provide access to bis-dihydro derivatives. The potential of bis-peptides like 203-4 for the controlled release of one peptide group should also be further investigated.

4.4.3 Towards tris-substituted fullereryl derivatives

The base-assisted transesterification of the fullereryl bis-iminoglycinate 189 has been routinely used in our laboratory to enhance the solubility profile of fullereryl derivatives in organic solvents\(^\text{108}\). As part of this thesis this reaction was further
investigated with the aim of halting the reaction after the first ester transesterification, which would provide the alcohol 205. This molecule has an ideal handle to couple additional functional groups, which can then be attached to the carbon spheroid to provide a trisadduct (Scheme 4.13). To this end, a solution of the trans-4 fullerenylidihydropyrrole 189 in THF/ethanol (3 : 1) was treated with anhydrous Na₂CO₃ and stirred at RT for 1 h. The reaction mixture was then filtered and the crude mixture reduced in vacuo before being subjected to silica gel column chromatography. This furnished the starting material 189 (51%) and the desired alcohol 205 in 41% yield.

Scheme 4.13: Selective transesterification of 189 provided the key intermediate 205.

Confirmation of the structure of 205 was obtained through analysis of its ¹H NMR spectrum with the presence of a 3H triplet (J = 6.9 Hz) at 1.44 ppm, which was coupled to a
Chapter 4: Multifunctionalised Fullerenyl Derivatives

2H quartet ($J = 6.9$ Hz) at 4.50 ppm, assigned to the CH$_3$ and CH$_2$ of the ethyl ester, respectively. The emergence of a 2H doublet ($J = 6.0$ Hz) at 4.59 ppm, which was coupled to a broad 1H triplet ($J = 6.0$ Hz) at 2.14 ppm were assigned as the benzyl alcohol CH$_2$ and OH protons, respectively. Further downfield at 5.43 ppm appeared a 2H singlet, which was assigned as the remaining benzylic CH$_2$. Examination of the $^{13}$C NMR spectrum of 205 supported the proposed structure with resonances at 14.2 and 63.2 ppm assigned as the CH$_3$ and CH$_2$ of the ethyl ester. Additionally, the fullerenyl sp$^3$ carbons were split into 4 peaks (81.45, 81.50, 82.10 and 82.15 ppm) indicating both the lack of symmetry and that the C$_{60}$ cage was di-substituted. This was supported by the two close resonances at 96.6 and 96.7 ppm assigned as the sp$^3$ carbons of the dihydropyrrole rings. Further confirmation of the structure was provided by analysis of the ESI-MS spectrum which showed a peak at $m/z$ 1343 assigned as the molecular ion (M+H)$^+$. The optimised conditions for the conversion of 189 to the mono-transester 205 were established by decreasing the reaction time from the original report (from 2 h,$^{109}$ to 1 h). This allowed for isolation of the desired alcohol 205 in 11% yield (Table 4.5, entry 2). Shortening the reaction time further to 30 min only marginally increased the yield of 205 to 16%. Decreasing the relative concentration of EtOH from 2 (THF): 1 (EtOH) to 3 (THF): 1 (EtOH) had a positive effect on the generation of the alcohol 205 with an increased yield of 41% realised after 1 h, along with the starting material 189 (51%) and the diethyl ester 199 (5%) (entry 4). It was also found that by increasing both the amount of base and reaction time the yield of the known trans-4 and cis-3 diethyl esters 199 and 200, could be enhanced from 50-55% to 80-85%, respectively.
Table 4.5: Base-assisted transesterification of 189.

<table>
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<th>199 (%)</th>
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<td>-</td>
<td>83</td>
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</tr>
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</table>

*All reactions were done at 1.3 mol/L of 189.*

Interestingly, despite trying all the conditions listed in Table 4.5, the corresponding mono-transesterified alcohol of the cis-3 regioisomer 190 was never observed. Obviously the less favoured regioisomer 190 was under more steric strain than the analogous trans-4 isomer 189, which could explain the increase in reactivity.

The alcohol 205 was then coupled to ethyl malonate via its acid chloride in the presence of pyridine at 0 °C for 1 h, to provide the malonate 206 in 91% yield (Scheme 4.13, Figure 4.7).
Confirmation of the structure of 206 was provided by analysis of its $^1$H NMR spectrum which indicated the presence of a singlet resonance at 3.38 ppm with a relative integration of 2H, indicative of the methylene protons of the malonate functionality. The additional 2H quartet at 4.17 ppm ($J = 7.2$ Hz) and 3H triplet ($J = 7.2$ Hz) at 1.22 ppm also supported the presence of the ethyl malonyl moiety.

Examination of the $^{13}$C NMR spectrum of 206 indicated successful addition of the ethyl malonate moiety with the presence of a peak at 41.7 ppm assigned as the malonate methylene carbon (Figure 4.8). Further upfield, the resonances at 160.5 and 160.6 were assigned to the imine carbons while the peaks at 162.2, 162.3, 166.40 and 166.45 ppm represented the carbonyl groups of the four esters groups. Confirmation of the structure of
206 was provided by ESI-MS analysis with a peak at m/z 1455, assigned as the molecular ion (M+H)^+.

![Figure 4.8: 13C NMR spectrum (CDCl3, 75 MHz) of 206.](image)

The malonate 206 was subjected to standard Bingel reaction conditions (206, 1 equiv.; CBr₄, 1.2 equiv.; DBU, 2.2 equiv.) in CH₂Cl₂ at RT for 14 h, at which time the solution was reduced in volume and then applied to a silica gel column (Scheme 4.14). Elution with CH₂Cl₂ afforded two trisadducts 207a-b in 8% yield. However, the majority of material remained on the column and required elution with MeOH to be removed, this polar material was unable to be identified due to extensive line broadening of its ¹H NMR spectrum. Despite having large quantities of this material (>100 mg) no sensible data from ¹³C NMR or ESI-MS analysis was obtained.
Chapter 4: Multifunctionalised Fullerenyl Derivatives

Scheme 4.14: Synthesis of the tris-adducts 207a-b.

The first adduct eluted was the minor isomer (2%) and its $^1$H NMR spectrum exhibited the required four 1H doublets (4.78, 5.31, 5.42, and 5.53 ppm all with $J = 11.5$ Hz) corresponding to the four diastereotopic benzylid protons in 207a (Figure 4.9). Further evidence of the structure was provided by the loss of the resonance corresponding to the activated methylene protons (3.38 ppm) of the malonate group in 206. Support of the structure was provided by its ESI mass spectrum which showed a peak at $m/z$ 1453 assigned as the molecular ion (M+H)$^+$. Unfortunately this low yielding reaction did not allow for sufficient quantities of the adduct for a $^{13}$C NMR spectrum to be acquired.

The second isomer (6%) to be eluted (207b) showed the necessary four 1H doublets (4.87 ($J = 11.2$ Hz), 5.04 ($J = 10.5$ Hz), 5.64 ($J = 11.2$ Hz) and 5.77 ($J = 10.5$ Hz)) assigned as the diastereotopic benzylid protons in its $^1$H NMR spectrum (Figure 4.10). Analysis of its $^{13}$C NMR spectrum indicated the presence of the two ethyl esters with resonances at 14.3, 14.4 ppm and 63.0, 63.2 ppm representing the CH$_3$ and CH$_2$ resonances, respectively. One of the fullerene sp$^3$ carbons attached to the malonate moiety was visible at 78.0 ppm. The other resonance was suspected to be underneath the deuterated chloroform signal. It should be noted that there was an insufficient quantity of the product to allow a good signal to noise ratio and thus observe every expected resonance. The
fullerene sp$^3$ carbons, especially those part of a cyclopropyl ring have long relaxation times (10-15 seconds)$^{163}$ hence to see these resonances clearly it is necessary to increase the delay between pulses to 5 seconds (the normal T2 delay setting is 1 second so about 5 X longer). This resulted in a longer acquisition time, but was deemed necessary so that the sp$^3$ resonances could be seen. Confirmation of both the regioisomers of 207 was provided by examination of their ESI mass spectra, which both showed peaks at m/z 1453, assigned as their molecular ions (M+H)$^+$.  

**Figure 4.9:** $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 207a, inset shows the resonance assigned to the diastereotopic benzylic protons. X denotes an unknown contaminant present in the CH$_2$Cl$_2$ used in the purification procedure.
Despite attempts to optimise the reaction conditions (stoichiometry of reagents, time, concentration) the yields of the trisadducts 207 could not be further enhanced. This was expected to be due to the considerable steric influence of the diphenylhydropyrrole moiety attached at the trans-4 position of the carbon spheroid. Previous work in our laboratory has shown that the addition of the malonate diphenylimine tether 208 to C_{60} under Bingel reaction conditions resulted in exclusive formation of the e-edge regioisomer 209 (Scheme 4.15).\textsuperscript{164} Since this position is somewhat hindered by the ethyl ester of the dihydropyrrole in 206 it was thought likely that addition to this junction would be less favoured. Additionally, this explains the poor yield of the reaction, with the favoured e-edge position being blocked the tether must find alternative conformations to add to the C_{60} cage.
**Scheme 4.15:** Addition of 208 to fullerene under Bingel conditions provided the $e$-edge isomer 209 exclusively.

Future direction for this section of work would include using methanol for the initial ester transposition, which would allow additional space to access to the $e$-edge position of the cage in the attachment of the third moiety to the $C_{60}$ cage. Also the synthesis of a longer tether to alleviate the current steric issues should be examined.

### 4.4.4 Regio and stereochemical evaluation of a base assisted cycloaddition of a tethered iminoglycinate to [60]fullerene

As previously shown, the base assisted cycloaddition of tert-butylidene glycinate 138 to [60]fullerene furnished the *cis*-fulleropyrrolidine 121 in 64% yield (Scheme 4.16). This reaction was of sufficiently high yield to warrant further investigation into using this methodology for the construction of bis- and higher ordered $C_{60}$ derivatives.

**Scheme 4.16:** Synthesis of 121.
Chapter 4: Multifunctionalised Fullerene Derivatives

Therefore a suspension of the known trifluoroacetate salt 187, 108, 109 MgSO₄ and triethylamine in CH₂Cl₂ was treated with pivaldehyde and the reaction mixture was stirred at RT for 16 h, providing the bis-imine 210 in a 67% yield (Scheme 4.17).

![Scheme 4.17: Synthesis of bis-addend 210.](image)

Analysis of the ¹H NMR spectrum compound 210 indicated the presence of a 2H singlet at 7.57 ppm assigned as the imine protons. Further upfield at 4.20 ppm appeared a 4H singlet, a characteristic chemical shift corresponding to the doubly activated methylene protons, while the strong 18H singlet at 1.10 ppm implied the presence of the tert-butyl groups. Examination of its ¹³C NMR spectrum further supported the structural assignment of 210 with downfield resonances at 177.2 and 169.9 ppm attributed to the imino carbons and carbonyl esters respectively. Confirmation of the structure was provided by ESI-MS analysis, which showed a peak at m/z 389 assigned as the molecular ion (M+H)⁺.

When the equivalents of the starting aldehyde 211 was reduced to 1.0 equiv. the mono-tert-butylidene 212 was synthesised in 66% yield (Scheme 4.17). Proof of the structure of 212 was provided by analysis of the ¹H NMR spectrum, which showed a 9H singlet at 1.10 ppm assigned as the tert-butyl group. Further downfield a 2H singlet at 3.48 ppm was assigned as the methylene protons adjacent to the free amine, while a 2H singlet
at 5.16 ppm was assigned to the remaining benzylic protons. Confirmation of the structure was provided by analysis of the ESI mass spectrum, which showed a peak at \( m/z \) 321 assigned as the molecular ion (M+H)

The \textit{meta}-tethered bis-imine 210 was treated with a solution of [60]fullerene and 210 in toluene followed by DBU (Scheme 4.18). The reaction mixture was stirred at RT for 16 h, before the solution was concentrated \textit{in vacuo} and the crude residue subjected to silica gel column chromatography. Elution with CH\(_2\)Cl\(_2\) provided the bis-adducts, with \(^1\)H NMR analysis of this mixture indicating the presence of at least five isomeric products. The large number of products made the separation process very tedious, decreasing the overall yield considerably; in fact only one isomer was isolated in sufficient quantity and purity to allow extensive characterisation.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme418.png}
\caption{Scheme 4.18: Base-assisted cycloaddition of 210 to fullerene provided a complex mixture of isomers.}
\end{figure}

Proof of the structure of this isomer of 213 was provided by analysis of its \(^1\)H NMR spectrum, which showed two 2H singlets at 4.55 and 5.26 ppm assigned as the methine protons \( \alpha \) to the \textit{tert}-butyl and ester (tether) groups. The two 2H doublets (\( J =11.4 \text{ Hz} \)) at 4.99 and 5.27 ppm were assigned as the diastereotopic benzylic protons. Clearly an element of symmetry must exist. This was supported by analysis of the \(^{13}\)C NMR spectrum (Figure 4.11), which showed 28 full- and 3 half-intensity fullerene sp\(^2\) resonances, with the fourth
half-intensity resonance suspected to be obscured by a full-intensity peak. The four resonances at 128.7, 131.9, 132.0 and 133.9 ppm were assigned as the aromatic ring carbons, suggesting that the symmetry plane bisected the aromatic ring. The equivalence of the benzyl ipso carbons (133.9 ppm) also supports this conclusion, as shown in Figure 4.11. Further upfield between 82.7 and 67.4 ppm four discreet resonances were present (not including NMR solvent). However, it was anticipated that five resonances would appear in this region, the “missing” resonance was assigned to the fullerenyl sp\(^3\) carbon β to the tert-butyl group and was suspected to have been obscured by the large NMR solvent peak. Confirmation of the general structure was provided by analysis of the ESI mass spectrum, which showed a peak at \(m/z\) 1108 assigned as the molecular ion (M\(^+\)).

Based on symmetry information gathered from the \(^{13}\)C NMR spectrum the number of possible regioisomers was reduced to cis-1, cis-2 and trans-4. The cis-1 regioisomer was disregarded for steric reasons, without further spectroscopic evidence the products regiochemistry can be narrowed to either cis-2 or trans-4. The stereochemistry around the pyrrolidine moieties must be cis,cis or trans,trans to maintain the symmetry plane. Since no coupling was observed between the methine protons, as observed earlier in the cis-fulleropyrrolidine 121 (Chapter 3, Section 3.5.1) it was thought likely the stereochemistry was trans,trans. This was supported by analysis of the ROESY spectrum, which failed to show cross-peaks between the methine protons.
Figure 4.11: $^{13}$C NMR (CDCl$_3$, 75 MHz) of 213, with inset of the fullerényl sp$^2$ chemical shift region.

To unambiguously determine the regiochemistry of this compound a 2D-INADEQUATE spectrum would need to be acquired. Since the yield of this reaction was poor (mostly due to the purification) and the use of the expensive $^{13}$C-enriched C$_{60}$ was required to enable a reasonable signal to noise ratio, it was decided to not pursue this line of synthesis any further.
4.5 Future directions and conclusions

The reaction outcome for the addition of tethered bis-adducts 183 and 184 to [60]fullerene under Bingel reactions conditions were found to be fullerenylidihydropyrroles and not the previously reported methano[60]fullerene derivatives. The reductive ring-opening of 189 was achieved albeit in low yield, likewise the ring-opening of the diester 200 was also realised. The first reported fullerenyl bis-peptide was also described, along with a procedure to reductively eliminate one peptide.

This work also identified several promising methods for the potential synthesis of trisadducts including the alcohols 193 and 205. Additionally, preliminary work was done for the construction of tethered “mixed” iminoglycinates, which could potentially provide access to new fullerenyl derivatives.
Chapter 5: Characterisation and Mechanistic Study of Methano[60]fullerenes

5.1 [60]Fullerene and mass spectrometry

With fullerény chemistry in its infancy there is a need for new tools for structural elucidation to complement existing techniques. There is currently a heavy reliance on comparative methods for the determination of the regiochemistry of multifunctionalised fullerény derivatives such as UV-vis spectroscopy, which is routinely used to determine regiochemistry.\textsuperscript{165} The difference in UV-vis spectra for different regioisomers can be ambiguous and open to bias. NMR is an undeniably powerful tool for structural elucidation, however, the lack of hydrogen atoms on the fullerény cage, together with the large quantity of material required for \textsuperscript{13}C NMR analysis and often poor solubility in organic solvents can limit the spectral information gathered. Little work has been conducted into the use of comparative techniques to determine functionality, which would be of interest to fullerény chemists as mistakes in functional group identification have been known to occur.\textsuperscript{94, 128}

Mass spectrometry (MS) was instrumental in the discovery of fullerény\textsuperscript{2} with photoionisation TOF-MS used to detect \textit{C}$_{60}$ generated from the pulsed nozzle/laser vaporization of graphite technique.\textsuperscript{1} Previously fullerény and derivatives thereof, have been analyzed using FAB\textsuperscript{166, 167} and MALDI-TOF\textsuperscript{168, 169} MS, however problems with the solubility of the sample in the matrix has commonly been encountered and has hampered spectral acquisition. These methods typically provide limited molecular weight information, and often in the case of fullerény derivatives, where no protonation, deprotonation or cation attachment site exists, the only peak observed in the mass spectrum corresponds to pristine fullerény.\textsuperscript{170} In fact, the sensitive LD-MS technique has also been reported to cause significant fragmentation of fullerény derivatives leading to problems in interpretation of the respective spectra.\textsuperscript{171} The first use of ESI-MS on fullerény was
achieved by addition of a tagging agent (diazo-crown ether).\textsuperscript{172} Until recently soft ionization has proven difficult with many fullerenyl derivatives, due largely to the poor solubility of fullerenyl derivatives in polar solvents. Consequently the use of tandem MS for structural elucidation of fullerenyl derivatives has received little attention. Indeed, to the best of our knowledge, no significant fragmentation study of fullerenyl derivatives has been reported. The limited work published focuses on using a large excess of a nucleophile known to attack the fullerenyl cage and subsequently determination of the number of times the cage has been substituted by the nucleophile\textsuperscript{166, 173} and the distribution\textsuperscript{166} of the level of substitution. Therefore the aim of this study was to find a suitable solvent system and instrument settings to allow for detection of fullerenyl derivatives in the mass spectrometer. Additionally, tandem mass spectrometry would also be carried out on fullerenyl derivatives to examine if different functional groups provided different fragmentation patterns.

### 5.2 Methano[60]fullerene

As a preliminary study, the structurally well-characterised methanofullerenes \textit{70a-c} were examined (Scheme 5.1). Synthesis of these derivatives was achieved using the commercially available malonates \textit{214a-b}, while ethyl methyl malonate (\textit{214c}) was synthesised using a literature procedure.\textsuperscript{111} Each malonate was then independently subjected to Bingel reaction conditions to afford their corresponding methanofullerene.
Chapter 5: Characterisation and Mechanistic Study of Methano[60]fullerenes

[Diagram of a molecule with labels]

Scheme 5.1: Synthesis of methanofullerenes 70a-c.

As previously noted, the main problem encountered with MS (including ESI-MS) studies on C_{60} derivatives was the poor solubility profile of these relatively non-polar compounds in polar solvents. Hence, various solvent systems were examined to find a mixture that would allow for the ionisation and solubilisation of the fullerényl derivatives. The most consistent results were obtained using a CHCl₃/methanol (2 : 1) mixture. Typical instrument settings were spray voltages between 4 – 6 kV, capillary temperature 270 °C and sheath gas flow rates at 10 (arbitrary units). Figure 5.1 shows a negative ion ESI mass spectrum of the methanofullerene 70a and represents a typical spectrum for this compound type. The zoom scan (Figure 5.1, top right-hand corner) allowed for examination of the isotopic pattern and determination of the molecular ion species present, i.e. deprotonated [M-H]⁻ versus radical anion M⁻ molecular ions. In this example, and all other methano[60]fullerenes examined in this study the molecular ion observed was exclusively the radical anion.

Notably, higher mass compounds shown in the full spectrum (Figure 5.1), m/z 895 (70a+O)⁻ and m/z 911 (70a+O₂)⁻ represent oxidised species of the compound of interest and were speculated to be a direct result of the ionisation process in the presence of oxygen. No evidence of such structures is present in the ^{13}C NMR spectrum of 70a prior to injection.
into the mass spectrometer. Oxidised species of [60]fullerene have been previously observed in the mass spectrometer.\textsuperscript{174} Additionally, it was found that when pristine [60]fullerene was subjected to this ionisation process oxidised species were also observed.

![Graph](diagram.png)

**Figure 5.1**: Electrospray mass spectrum of methano[60]fullerene 70a with zoom scan inset.

Surprisingly, the calculated isotopic pattern in the ESI-MS of 70a did not match the observed, for any species examined. Most notably, the measured abundance of the \( m/z \) 879 ion was 89\% of \( m/z \) 878 in contrast to the 73\% abundance calculated based on an elemental composition of \( C_{67}H_{10}O_4 \). This was thought to be a result of hydrogen atom abstraction from the methanol or chloroform, used to dissolve the sample, and subsequent addition to the fullerene cage thus leading to [M+H]' species, a similar trend was also observed for 70b and 70c (the [M+H]' species were tentatively assigned as structures 215b' and 215b'' Figure 5.2 and Appendix). To test this hypothesis, solutions of 70a-c in chloroform/deuterated methanol (CD\(_3\)OD) (2 : 1) were subjected to negative ion mode ESI.
The mass spectrum showed a change in peak distribution consistent with an increase of a single mass unit, supporting the notion that hydrogen atom abstraction from the methanol was the cause of the deviation of the observed isotopic pattern to that predicted, as exemplified in zoom scans of 215b (Figure 5.2, Table 5.1). The precise position of the proton or deuterium atom, from the methanol, on the cage is uncertain. However, it appeared that pristine C_{60} also abstracts a hydrogen atom from methanol suggesting that the ring-opened cyclopropyl structure may not be correct.

**Figure 5.2**: a) Zoom scan of the M$^+$ of 70b when run in a CHCl$_3$/CH$_3$OH (2 : 1). b) Zoom scan of the M$^+$ of 70b when run in a CHCl$_3$/CD$_3$OD (2 : 1).
### Table 5.1: Calculated and observed isotopic ratios of molecular radical anion of 70b.

<table>
<thead>
<tr>
<th>m/z</th>
<th>Calculated</th>
<th>Observed * (°)</th>
<th>Observed † (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>906</td>
<td>100</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>907</td>
<td>74.9</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>908</td>
<td>28.5</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>909</td>
<td>7.3</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>910</td>
<td>1.4</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

*Experimentally observed isotopic ratio. † Sample 70b in CHCl₃/CH₃OH was subjected to ESI-MS. ‡ Sample 70b in CHCl₃/CD₃OD was subjected to ESI-MS.

With a general procedure developed for acquiring mass spectra of methano[60]fullerenes with a good signal to noise ratio in the negative ion mode with sufficient ion counts (typically 10³) established, a preliminary study into the fragmentation patterns of malonate derived methano[60]fullerenes was conducted.

As shown in Figures 5.1 and 5.2 when methano[60]fullerenes 70a and 70b, which have molecular weights of 878 and 906 Da, respectively, were subjected to ESI-MS, in the negative ion mode, the spectra displayed the radical anions M⁺ and [M+H]⁺. The absence of the deprotonated species [M-H]⁻ (m/z 877 and 905) was due to the lack of acidic protons on the molecules. The structure of the molecular anion M⁺ were speculated to be of the general type 215a (Figure 5.1), which was thought likely due to [60]fullerene’s inherent ability to accept electrons. In fact, the electron affinity of C₆₀ has been experimentally determined as 259 KJ/Mol (2.689 eV).¹⁷⁵

The peak at m/z 878.1 was then mass selected and fragmented to generate the MS² spectrum (Figure 5.3). The peak at m/z 834 corresponds to a loss of 44 Da indicating a loss of CO₂. For this to occur a rearrangement must take place whereby one of the ethyl groups of 215a is detached, carbon dioxide extruded, and the ethyl group then re-attached. This process may occur as displayed in Scheme 5.2, whereby the ethyl radical can open the...
cyclopropyl ring of the ion dipole complex 216a, to form the radical anion 217a. The absence of a peak at \( m/z \) 749 \([\text{C}_{60}\text{CH}_2\text{CH}_3]^+\) and the observation of a peak at \( m/z \) 733 provides some evidence that the ethyl radical re-attaches to the bridge-head carbon rather than onto the cage, although this can not be excluded (Figure 5.3). Ion dipole complexes like 216a are well-studied and commonplace in gas phase reactions.

The direct dissociation of the complex 216a would give rise to the ester 218a (\( m/z \) 805), the observation of an ion at this mass provides further evidence for this mechanism.

**Figure 5.3:** MS\(^2\) of \( m/z \) 878 of 70a. The isolation width was increased to enhance the ion count, however this causes some of the M+1 isotope to be included in the fragmentation.
Scheme 5.2: Proposed fragmentation pathway of 70a.

This proposed pathway was supported by examination of the MS² of the tert-butyl ethyl malonyl methano[60]fullerene 70b, which under comparable ionisation conditions, displayed a peak at m/z 862 assigned as the tert-butyl substituted ethyl ester 217b, the direct analog of 217a, at less than 5% relative abundance at 50x magnification (Figure 5.4a). Additionally, the more stable ‘Bu radical is also more likely to be lost as a neutral species as shown by; 1) m/z 805 –[CO₂ + ‘Bu] being more abundant than m/z 833 –[CO₂ + Et], and 2) –[CO₂ + ‘Bu] is much more abundant than –CO₂ compared to –[CO₂ + Et] versus –CO₂ in Figure 5.3. Additional evidence for the stability of the ‘Bu radical was provided by the small, but observable, m/z 849 (‘Bu⁺), no such –CH₃ or –CH₂CH₃ ions were observed for the other malonates.

Conversely the methyl ethyl malonyl methano[60]fullerene 70c, showed a similar proportion of the decarboxylated intermediate (217c) to that of 70a (Figure 5.4b, m/z 820). This was expected under the mechanism proposed, as the tert-butyl radical would be more stable than the ethyl, while the methyl would be less stable but also less likely to form in
the first place, hence the extent of decarboxylation was expected to be similar to that seen in the ethyl ester case (70a). The observation that \( m/z \) 791 (\([-\text{CO}_2 + \text{Et}\]) was more abundant than \( m/z \) 805 (\([-\text{CO}_2 + \text{Me}\]) (Figure 5.4b) further supported the relative stability to be \( \text{Me}^* < \text{Et}^* < \text{tBu}^* \).

![Figure 5.4: a) MS² of \( m/z \) 906 of 70b. b) MS² of \( m/z \) 864 of 70c.](image)

The peak observed at \( m/z \) 760 was common to all of the malonates examined and is speculated to be the ketene 219, which was proposed to occur via the mechanism outlined in Scheme 5.3.
**Scheme 5.3**: The peak \( m/z \) 760, which was observed for all malonates is proposed to be the ketene 219.

Figure 5.5 displays the MS\(^3\) spectrum of \( m/z \) 834 of 70a, that is the \( m/z \) 878 was selected then fragmented (MS\(^2\), Figure 5.3) then from this \( m/z \) 834 was selected then fragmented (MS\(^3\)). This spectrum showed that the most abundant fragments are \( m/z \) 761 and 790, which correspond to the ethyl and diethyl methanofullerene anions 220a and 221a, respectively (Scheme 5.4). These fragments arise from the loss of CO\(_2\) (-44 Da), 221a, and the combined loss of CO\(_2\) and Et\(^+\) (-73 Da), 220a, and as such are directly analogous to the neutral losses observed from the precursor ion (\( m/z \) 878) in Figure 5.3. The similarity in the fragmentation pattern of \( m/z \) 878 and its product ion, \( m/z \) 834, provide evidence of significant similarities in the structure of these ions (*i.e.* 215a and 217a).
Figure 5.5: MS$^3$ of m/z 834 of 70a.

Scheme 5.4: Proposed fragmentation pathway of 70a.
The product ion at \( m/z \) 805 was observed for all the methanofullerenes investigated (Scheme 5.2, Figures 5.3 and 5.4). This ion arises from the loss of CO\(_2\) and an associated Me, Et or \(^1\)Bu radical and thus is an even electron ion, which has the proposed structure (218a). Figure 5.6 shows the MS\(^3\) spectrum of this ion, which is identical regardless of the precursor species confirming that a common structure was formed in each case. Losses of CO\(_2\) and the combined loss of CO\(_2\) and CH\(_2=\)CH\(_2\) to form C\(_{61}\)H\(^+\) (\( m/z \) 733), along with the ubiquitous formation of C\(_{60}\) (\( m/z \) 720) are all consistent with the proposed structure.

![Figure 5.6](image)

**Figure 5.6:** Fragmentation pattern of intermediate anion 218a.

To provide further support for the structure of intermediate 218a, the methanofullerene 222 was synthesised by the addition of the sulfonium ylide 223 to C\(_{60}\) in a literature procedure (Scheme 5.5).\(^{116}\) Then 222 was exposed to the same ionisation conditions as the other methanofullerenyl derivatives. It was expected that the proton attached to the bridgehead carbon would be sufficiently acidic to allow the generation of the deprotonated species \([\text{M-H}]^-\), whose fragmentation profile could then be directly compared to that found in the malonate derivatives, thereby strengthening the postulated mechanism of fragmentation.
When 222 was subjected to ESI-MS only traces of the [M-H]- molecular anion (m/z 805) was observed with the radical anion (M*) dominating (m/z 806). The addition of NH3 to the solution before spraying into the ionisation source did not improve the peak strength enough to allow for mass selection and subsequent fragmentation of the m/z 805, [M-H]- ion (Figure 5.7a). Nevertheless isolation of the molecular ion (m/z 806, M*) and fragmentation showed the same spectrum as seen in the malonyl derivatives, specifically, the loss of CO2 and the combined loss of CO2 and Et, except for a shift up of one mass unit (Figure 5.7b). This accounts for the proton on the bridgehead carbon of the cyclopropyl ring. The peak at m/z 733, which is common to 70a-e and 222, occurs by deprotonation of 224 (Figure 5.6b). Radical anion 224 was expected to form by hydride donation from the ethyl group of 225, which was commonly observed in the malonyl fullerene derivatives examined. Importantly, this also indicates that the second ester group is not necessary for this mechanism.
Chapter 5: Characterisation and Mechanistic Study of Methano[60]fullerenes

5.3 Conclusions

To conclude, methano[60]fullerenes can be ionised in the absence of acidic or basic groups using conventional ESI-MS. Tandem mass spectra of the resulting $M^*$ appear to follow pathways consistent with their proposed structures, as shown in the general Scheme 5.6. This suggests that ESI-MS and tandem MS may prove a powerful tool for structure elucidation in fullerene chemistry. However, it must be acknowledged that this was a preliminary investigation and a greater sample size would need to be analysed before any definitive conclusion could be made. Therefore, work should be conducted on expanding
the number of derivatives and functional groups examined by tandem mass spectrometry with the goal of using MS$^2$ to identify functional groups.

The ESI-MS and MSMS data for 70a–e and 222 has been tabulated in Appendix 1.
Scheme 5.6: Proposed general fragmentation of methano[60]fullerene derivatives in tandem ESI-MS.
6.1 Conclusions

The research reported in this thesis has shown that the reaction products from the addition of $N$-(diphenylmethylene)glycinate esters to [60]fullerene under Bingel reaction conditions are diphenylfullerenyldihydropyrroles 106 rather than the previously reported methanofullerenyl derivatives 97. Mechanistic details were proposed to account for the formation of the [60]fullerenyldihydropyrroles and their reductive ring-opening products (Scheme 6.1).

Scheme 6.1: The addition of diphenyliminoglycinates 96 to fullerene under Bingel reaction conditions provided the diphenylidihydropyrroles 106.

Reductive removal of the benzhydryl group of the ring-opened fullerenyldipeptide 99a provided ethyl $\alpha$-fullerenylglycinate (111a), the first reported acyclic $\alpha$-substituted fullerenyldipeptide (Scheme 6.2). Subsequent amide coupling to N-protected amino acid chlorides provided fullerenyldipeptides, such as 129. Preliminary results indicate that the Fmoc protecting group can be removed from the N-terminus of a fullerenyldipeptide, under basic conditions, and the amine coupled to $N$-protected amino acids under standard EDCI/HOBt amide coupling conditions to deliver tripeptides, like 131, “capped” with fullerenylglycinate (Scheme 6.2). Notably, 111a was also shown to readily participate in intramolecular Mannich reactions with cyclohexanone, acetone and pivaldehyde, generating their corresponding fulleropyrrolidines.
Alternatively the [60]fullerenydihydropyrroles 106a,b were shown to be readily converted to the carboxylic acid 114 which could then be coupled to ethyl L-phenylalaninate to deliver the fullerenyldihydropyrrole peptide 115a in good yield. Unfortunately all efforts to ring-open 115a to form the peptide 116a were unsuccessful (Scheme 6.2).

Scheme 6.2: Synthesis of fullerenyl peptides.
A range of alkyl-, thio-, and aromatic-iminoglycinates were synthesised and subsequently subjected to Bingel reaction conditions in the presence of [60]fullerene in an effort to generate their corresponding methano[60]fullerenyl adducts. Despite concluding that all the iminoglycinates examined were unsuitable precursors for the generation of stable methano[60]fullerenyl derivatives, the reductive ring-opening of the unstable methano[60]fullerenyl derivative 147 afforded the more stable dihydrofullerenyl adduct 161. Conversely, when the fullerenyldihydropyrrole 148 was exposed to the reductive ring-opening conditions the cis-fulleropyrrolidine 121 was generated in good yield (Scheme 6.3).

Scheme 6.4: Reductive ring-opening of 147 afforded the dihydrofullerene 161.

The generation of a stable protected α-substituted methanofullerenyl amino ester was discovered when α-bromophthylglycinate (179) and [60]fullerene was subjected to Bingel reaction conditions, with methanofullerene 180 isolated in moderate yield (37%) (Scheme 6.4).
Scheme 6.4: Addition of 179 to fullerene under Bingel reaction conditions generated the methanofullerene 180.

The reaction products from the addition of tethered bis-N-(diphenylmethylene)glycinate esters to [60]fullerene under Bingel reaction conditions were found to afford bis-diphenylfullerenylidihydropyrroles and the not the previously reported bis-methanofullerenyl derivatives. The regiochemical outcomes remain as originally reported. The ring-opened tethered bis-dihydrofullerenes, trans-4 196 and the non-tethered, cis-3 201 were accessed from the bis-diphenylfullerenylidihydropyrroles 189 and 190, respectively, albeit it in low yield. Intriguingly, only a portion of the expected isomers were observed (Figure 6.1).

Figure 6.1: Bis-ring-opened derivatives 196 and 201.

Tether removal of the fullerenyl dihydropyrrole 189 to form the fullerenyl bis-carboxylic acid 202 and subsequent amide coupling to L-phenylalaninate esters delivered the first reported fullerenyl bis-peptides 203 and 204. Monotransesterification of 189 provided the key intermediate 205 for the synthesis of tris-
adducts. This was subsequently coupled to ethyl malonyl chloride, then subjected to Bingel reaction conditions to afford the trisadduct 207 as mixture of two separable regioisomers. However, the regiochemistry of these compounds was not determined as the overall reaction yields were poor and could not be further enhanced (Scheme 6.4).

Scheme 6.4: Treatment of the bis-acid 202 with phenylalaninate esters furnished fullerenyl bis-peptides 203 and 204. Addition of the malonate group of 206 to the fullerene cage afforded the tris-adduct 207 as a separable mixture of two regioisomers.

The base assisted bis-cycloaddition of a meta-tethered bis(tert-butylideneglycinate) 210 to [60]fullerene provided a complex mixture of isomers. Only one isomer (213) was successfully isolated, this was compound was narrowed down to either the trans,trans cis-2 or trans,trans trans-4 isomer of 213.

6.2 Future directions

The scope of the intramolecular Mannich reaction (Section 2.3.2) should be further examined using other aldehydes and ketones, which could be activated by the addition of a Lewis acid to promote iminium ion formation. Preliminary results indicate
that the Fmoc group in fullerenyl dipeptides like 129 can be removed under standard basic conditions and subsequent EDCI/HOBt mediated amide coupling appeared successful in producing a tripeptide (Scheme 6.2). Future work should involve optimisation and extension of this coupling reaction to include the addition of biologically active peptides.

Deprotection of the carboxyl group of 180 should be readily achieved using the established Lewis acid (BBr₃) method (Scheme 3.33). Carboxyl coupling should also be forthcoming, again, using the established methodology (EDCI/HOBt). Amine deprotection of 180 is anticipated to be less straightforward with typical conditions for phthyl-removal requiring primary or secondary amine bases, which may attack the electron-deficient fullerene cage. However within the literature there exist methods for the removal of phthyl-derived groups from primary amines, which could be slightly modified to be compatible with fullerene potentially providing access to α-fullerenyl peptides, whose biological and conformational properties could then be examined.

Larger peptides should be coupled to 202, to allow increased water solubility, hopefully leading to increased applications in biological systems. The potential of bis-peptides like 203–4 for the controlled release of one peptide group under reducing conditions should also be further investigated (Scheme 6.4).

The use of alcohols the 193 and 205 to access tris and higher substituted fullerenes should be examined. Additionally, preliminary work was done for the construction of tethered “mixed” iminoglycinates, which could also potentially provide access to new fullerenyl derivatives.
7. Experimental

Reagents and solvents were purchased reagent-grade and used without further purification. Toluene and THF were distilled from sodium benzophenone ketyl. DCM was stored over CaCl₂ and distilled from CaH₂. MeCN was distilled from potassium carbonate. [60] Fullerene was purchased from MER Corporation Tucson, Arizona AZ 85706, USA. All reactions were performed in standard glassware under an inert atmosphere of nitrogen unless otherwise specified. Flash column chromatography was performed using silica 60 (230-400 mesh, 0.040-0.063 mm) purchased from Merck. Petroleum spirit refers to a hydrocarbon fraction with a boiling point of 40-60 °C. Mass spectral data were recorded on a Shimadzu QP-5000 for CIMS data. ESMS were recorded on a VG Quattro-triple quadrupole via a direct insertion technique and an electron beam energy of 70eV and a source temperature of 200 °C. All fullerene derivatives were run on ThermoFinnigan LTQ (Waltham, MA) fitted with a conventional IonMax electrospray ionization source. Spectra were obtained by infusion of a standard solution in chloroform/methanol (2/1). Typical settings were spray voltages between 4 – 6 kV, capillary temperature 270 °C and sheath gas flow rates at 10 (arbitrary units). High resolution mass spectra (CI) were obtained using a QTOF mass spectrometer. ¹H NMR spectra were acquired on a Varian Unity 300 or 500 spectrometer at 300.1 and 499.9 MHz respectively, or a Bruker DMX-600 spectrometer at 600.2 MHz. ¹³C NMR spectra were acquired on Varian Unity 300 or 500 spectrometer at 75.4 and 125.0 MHz respectively, or a Bruker DMX-600 spectrometer at 150.9 MHz. Deuterated solvents CDCl₃, D₂O, C₆D₆, CD₃COCD₃, CD₃OD, CD₂Cl₂, C₄D₈O were obtained commercially (Sigma-Aldrich or Cambridge) and were greater than 99.5 atom % d. All chemical shifts are reported relative to TMS (δ 0.00).
The 2D INADEQUATE experiments for 10% $^{13}$C-enriched fullerene samples were performed on a Bruker DMX 600 spectrometer fitted with a Bruker TXI-XYZ $^1$H/$^{13}$C/$^{15}$N probe. The sample (ca. 16 mg) was dissolved in CS$_2$/CDCl$_3$ (6 : 4) (ca. 250 µL) in a Shigemi tube and the spectra were recorded at 288 K. A standard pure phase (States-TPPI) double quantum spectrum with power-gated proton decoupling was employed. A spectral width of 13020.8 Hz was used in both dimensions resulting in deliberate folding in F1, which will not cause any ambiguity of peak assignments. 2048 x 8192 Total points were collected in t1 and t2 respectively. A recycle delay of 9 seconds and 16 scans per increment were employed.

Order of assignment is chemical shift, multiplicity, integration, $J$ value, and assignment. All fullereryl sp$^2$ carbon signals were reported as a full resonance, e.g. (148.0), or as a half-intensity peak (148.0, (1/2 x C)) or as an integer of a full resonance (148.0, (2 x C)), which is termed a double intensity peak (coincidental peak overlap).

Throughout this experimental section cis and trans nomenclature was used for describing the NMR spectroscopic assignment of imines with the general structure shown in Scheme 7.1. Where cis and trans is referring to the positions of the imino-substituents R relative to the methylene carbon of the glycinate.

All weights were reported to 2 significant figures, with the following exception, when masses were over 10.0 g they were reported to 3 significant figures.

All new compounds have compound names in headings in italics. When a reference is provided in the title it signifies that this reference procedure was used. Conversely, when a reference is provided with NMR data it signifies that our data is in agreement with that already reported.
Chapter 7: Experimental

_Ethyl methyl malonyl methano[60]fullerene 70c_

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.082 mL, 0.56 mmol) was added at RT to a soln containing [60]fullerene (0.10 g, 0.14 mmol), carbon tetrabromide (0.059 g, 0.18 mmol) and ethylmethylmalonate (0.026 g, 0.18 mmol) in toluene (200 mL).

The soln was stirred for 12 h then concentrated _in vacuo_ to approximately half the volume. The crude residue was subjected to flash silica gel chromatography and elution with CH$_2$Cl$_2$/hexanes (1/1) followed by recrystallisation from CH$_2$Cl$_2$/hexane gave _70c_ as a fine black powder (0.058 g, 48%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.49, t, 3H, $J = 7.0$ Hz, CH$_2$CH$_3$; 4.10, s, 3H, OCH$_3$; 4.57, q, 2H, $J = 7.0$ Hz, CH$_2$CH$_3$. $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 14.4, CH$_2$CH$_3$; 54.2, OCH$_3$; 63.6, CH$_2$CH$_3$; 71.7, (CO$_2$Et)C(CO$_2$Me); (139.15, 139.2, 141.2 (2 x C), 142.05, 142.1, 142.4 (2 x C), 143.1, 143.15, 143.2 (2 x C), 143.24, 143.25, 144.0 (2 x C), 144.78 (2 x C), 144.8, 144.85 (2 x C), 145.0, 145.3, 145.35 (2 x C), 145.38, 145.4 (2 x C)) C$_{60}$sp$^2$; 163.7, CO; 164.3, CO. NB did obtain a high enough signal to noise ratio to observe the C$_{60}$sp$^3$ resonance. ESMS (-ve): $m/z$ 864 (100%, M$^-$) 100%.

_Ethyl $\alpha$-[N-(diphenylmethyl)amino]-1,9-dihydrofullereryl acetate 99a_

To a solution of _106a_ (0.030 g, 0.030 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C under an atmosphere of nitrogen was added dropwise boron trifluoride-diethyl etherate (0.043 g, 0.30 mmol) over 1 min. The reaction mixture was stirred for 15 min then THF (20 mL), sodium cyanoborohydride (0.019 g, 0.30 mmol) and glacial acetic acid (0.1 mL) were added and the solution was stirred for 30 min. The reaction mixture was then concentrated _in vacuo_, the residue redissolved in CH$_2$Cl$_2$ (40 mL) and washed
with a saturated NH₄Cl solution (10 mL). The organic phase was collected, dried (MgSO₄), filtered and concentrated under reduced pressure. The crude material was then subjected to silica gel column chromatography, elution with toluene/hexanes (1 : 1) afforded 99a (0.020 g, 68%) as a brown amorphous solid. The spectral data was identical to that reported.¹¹⁰ ¹H NMR (CDCl₃, 300 MHz): δ 1.32, t, 3H, J = 7.0 Hz, CH₃; 3.68, dd, 1H, J = 11.7, 3.3 Hz, NH; 4.39, m, 2H, CH₂; 4.96, d, 1H, J = 11.7 Hz, CHPh₂; 5.32, d, J = 3.3 Hz, CHCO₂Et; 6.89, s, 1H, C₆₀H; 7.20, m, 2H, ArH; 7.28, t, 2H, J = 10.4 Hz, ArH; 7.33, t, 2H, J = 10.4 Hz, ArH; 7.56, d, 2H, J = 10.4 Hz, ArH; 7.66, d, 2H, J = 10.4 Hz, ArH. ¹³C NMR (C₆D₆/CS₂, (3 : 2), 75 MHz): δ 14.9, 58.1, 61.8, 66.8, 68.1, 70.8, 128.0, 128.6, 129.2, 129.3, 136.5, 136.7, 136.8, 137.5, 139.7, 140.0, 140.8, 140.9, 141.9, 142.0, 142.01, 142.4, 142.6, 142.7, 142.9, 143.3, 143.5, 143.51, 143.6, 144.7, 145.0, 145.7, 145.72, 145.95, 145.97, 146.0, 146.5, 146.7, 146.71, 146.73, 147.38, 147.39, 147.4, 147.8, 152.9, 153.5, 154.4, 171.8. ESI-MS (+ve): m/z 990 (100%, M+H).

tert-Butyl α-[N-(diphenylmethyl)amino]-1,9-dihydrofullerenyl acetate 99b

Boron trifluoride(diethyl etherate (0.045 g, 0.32 mmol) was added dropwise over 1 min to a solution of 106b (0.032 g, 0.032 mmol) in CH₂Cl₂ (20 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 15 min before THF (15 mL), sodium cyanoborohydride (0.021 g, 0.32 mmol) and glacial acetic acid (0.1 mL) were added. The reaction mixture was stirred for 30 min before being concentrated under reduced pressure and subjected to silica gel column chromatography. Elution with CH₂Cl₂/hexanes (1 : 1) furnished the title compound 99b (0.018 g, 56%) as a brown amorphous solid. The spectral data was identical to that
Ethyl (5,5-diphenylfullerenyldihydropyrrole)-2-carboxylate 106a

Method 1

DBU (0.082 mL, 0.56 mmol) was added at RT to a solution of [60]fullerene (0.10 g, 0.14 mmol), carbon tetrabromide (0.059 g, 0.18 mmol) and ethyl N-(diphenylmethylene)glycinate (0.049 g, 0.18 mmol) in toluene (200 mL). The solution was stirred for 3 h then concentrated in vacuo to approximately half the volume. The crude residue was subjected to flash silica gel chromatography and elution with CH$_2$Cl$_2$/hexanes (1 : 1) followed by recrystallisation from CH$_2$Cl$_2$/hexane gave 106a (0.081 g, 59%) as a fine black powder. The spectral data was identical to that reported.$^{110}$

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.53, t, 3H, J = 7.0 Hz, CH$_3$; 4.63, q, 2H, J = 7.0 Hz, CH$_2$; 7.40, t, 2H, J = 7.3 Hz, ArH; 7.52, t, 4H, J = 7.3 Hz, ArH; 8.10, d, 4H, J = 7.3 Hz, ArH. $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ 14.4, CH$_3$; 62.8, CH$_2$; 82.7, C$_{60}$sp$^3$; 82.73, C$_{60}$sp$^3$; 95.9, N$_2$Ph$_2$; 128.2, ArC; 128.3, ArC; 129.7, ArC; (134.6, 136.5, 139.1, 139.6) C$_{60}$sp$^2$; 140.8, ArC1,1'; (141.2, 141.69, 141.71, 141.8, 142.3, 142.6, 142.7, 142.9, 144.06, 144.1, 144.7, 144.96, 145.0, 145.25, 145.3, 145.4, 145.7, 145.81, 145.82, 146.3, 146.8 (1/2 x C), 146.9 (1/2 x C), 147.5, 148.5, 153.1) C$_{60}$sp$^2$; 159.9, C=N; 161.8, CO. ESI-MS (+ve): m/z 986 (100%, M+H).
Method 2

To a solution of [60]fullerene (0.043 g, 0.06 mmol) and ethyl N-(diphenylmethylene)glycinate (0.032 g, 0.12 mmol) in chlorobenzene (30 mL) was added manganese (III) acetate dihydrate (0.032 g, 0.12 mmol). The reaction mixture was heated at reflux under an inert atmosphere of nitrogen gas for 1 h. The crude mixture was reduced in volume to approximately half then subjected to flash silica gel chromatography, elution with CH$_2$Cl$_2$/hexanes (3 : 2) provided the title compound 106a (0.015 g, 25%) as a fine black powder. Which was spectroscopically identical to that reported for Method 1.

tert-Butyl (5,5-diphenylfullerenyldihydropyrrole)-2-carboxylate 106b $^{110}$

[Chemical structure image]

DBU (0.18 mL, 1.2 mmol) was added at RT to a solution of [60]fullerene (0.22 g, 0.31 mmol), carbon tetrabromide (0.13 g, 0.39 mmol) and N-(diphenylmethyleneglycinate) tert-butyl ester (0.11 g, 0.40 mmol) in toluene (250 mL). The solution was stirred for 2 h, then concentrated in vacuo and subjected to flash silica gel chromatography. Elution with CH$_2$Cl$_2$/hexanes (3 : 2) provided the title compound 106b (0.14 g, 46%) as a brown amorphous solid. The spectral data was identical to that reported.$^{110}$

$^1$H NMR (CDCl$_3$, 300MHz): δ 1.60, s, 9H, CH$_3$; 7.31, t, 2H $J = 7.5$ Hz, ArH4,4'; 7.42, t, 4H, $J = 7.5$ Hz, ArH3,3',5,5'; 8.05, d, 4H, $J = 7.8$ Hz, ArH2,2',6,6'.

$^{13}$C NMR (CDCl$_3$, 75MHz): δ 30.3, CH$_3$; 82.7, 2xC$_{60}$sp$^3$; 84.3, C(CH$_3$)$_3$; 96.0, CPh$_2$; 128.6, 130.0, 134.5, 136.8, 139.5, 140.0, 141.7 (2 x C), 142.15, 142.2 (2 x C), 142.6, 142.7, 143.1, 143.3, 144.5, 145.1, 145.4, 145.5, 145.7, 146.1, 146.2 (2 x C), 146.6, 147.8, 149.3, 153.7, CN; 162.4, CO. ESI-MS (+ve): m/z 1013 (100%, M$^{+}$).
Using higher field NMR this resonance is shown to actually be two separated by ~0.03 ppm.

**Ethyl N-(diphenylmethylglycinate) 110**

\[
\text{Ph} \quad \text{NH} \quad \text{O} \\
\text{Ph} \quad \text{O} \quad \text{CO} \\
\]

To a solution of ethyl N-(diphenylmethylene)glycinate (0.05 g, 0.19 mmol) in methanol (10 mL) was added sodium cyanoborohydride (0.013 g, 0.21 mmol). The mixture was then stirred vigorously for 16 h under an atmosphere of nitrogen before being concentrated under reduced pressure and then subjected to column chromatography. Elution with CH\textsubscript{2}Cl\textsubscript{2}/hexanes (4 : 1) furnished 110 (0.038 g, 75 %) as fine cream coloured crystals. The spectral data was identical to that reported.\textsuperscript{179} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 1.26, t, 3H, \(J = 7.3\) Hz, CH\textsubscript{3}; 3.38, s, 2H, COCH\textsubscript{2}; 4.18, q, 2H, \(J = 7.3\) Hz, OCH\textsubscript{2}CH\textsubscript{3}; 4.89, s, 1H, CH; 7.23, m, 2H, ArH; 7.30, m, 5H, ArH; 7.41, m, 3H, ArH. ESI-MS (+ve): 270 (100%, M+H).

**Ethyl \(\alpha\)-(1,9-dihydrofullereryl)glycinate 111a**

\[
\text{H}_2\text{N}_2\text{O} \quad \text{Et} \\
\]

To a solution of 99a (0.10 g, 0.10 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL) was added TFA (4.0 mL) and triethylsilane (0.030 g, 0.26 mmol) and the suspension was heated at reflux for 30 min. The cooled solution was then directly added to a silica gel column. Elution with CH\textsubscript{2}Cl\textsubscript{2} afforded 111a, the solution was washed with a sat. NaHCO\textsubscript{3} solution (5 x 20 mL), dried (MgSO\textsubscript{4}), filtered and the solution was then used immediately in the subsequent reactions. ESI-MS (+ve): \(m/z\) 824 (100%, M+H).
5,5-Diphenylfullerenyldihydropyrrole-2-carboxylic acid 114

*Method 1*

To a vigorously stirred solution of 106a (0.10 g, 0.10 mmol) in anhydrous CH₂Cl₂ (50 mL) at −10 °C was added dropwise BBr₃ (0.8 mL (1.0M solution in CH₂Cl₂), 0.8 mmol). The mixture was then left for 15 h at RT, before slowly adding water to quench the excess reactant. The organic phase was then dried (MgSO₄) and reduced *in vacuo* to provide the title compound 114 (0.027 g, 28%) as a brown amorphous solid. ¹H NMR (300 MHz, CDCl₃): δ 7.36, d, 2H, J = 7.2 Hz, ArH4, 4'; 7.47, t, 4H, J = 7.2 Hz, ArH3, 5, 3', 5'; 8.07, d, 4H, J = 7.2 Hz, ArH2, 2', 6, 6'; 9.14, s, 1H, CO₂H. ESI-MS (-ve): m/z 956 (100%, M-H).

*Method 2*

To a solution of 106b (0.15 g, 0.15 mmol) in anhydrous CH₂Cl₂ (10 mL) at RT was added TFA (2 mL) and the solution was stirred for 3 h before hexanes were added to precipitate the title compound 114 (0.086 g, 61%) as a brown solid. This material was spectroscopically identical to that reported above.

**Ethyl 2-(5',5'-diphenylfullerenyldihydropyrrole-2'-carboxamido)-3-phenylpropanoate 115a**

To a suspension of 114 (0.070 g, 0.073 mmol) in CH₂Cl₂ (50 mL) was added HOBT (0.011 g, 0.080 mmol) and EDCI (0.015 g, 0.080 mmol) and the mixture was stirred for 15 min before a solution of L-phenylalanine ethyl ester hydrochloride (0.018 g, 0.080 mmol) and Et₃N (0.010 g, 0.10 mmol) in CH₂Cl₂ (2 mL) was added dropwise. The resulting solution was stirred at RT for a further 30 min before the
solvent was removed under reduced pressure. The crude residue was then subjected to flash silica chromatography, elution with CH₂Cl₂ provided the title compound 115a (0.051 g, 62%) as brown solid. ¹H NMR (CDCl₃, 300 MHz): δ 1.30, t, 3H, J = 7.2 Hz, CH₃; 3.26, dd, 1H, J = 13.8, 6.3 Hz, CHHPh; 3.42, dd, 1H, J = 13.8, 6.3 Hz, CHHPh; 4.26, m, 2H, OCH₂; 5.13, m, 1H, CH; 7.26, m, 3H, ArH; 7.38, m, 3H, ArH; 7.47, m, 2H, ArH; 7.57, m, 3H, ArH; 8.00, m, 4H, ArH; 8.21, bd, 1H, J = 8.7 Hz, NH. ¹³C NMR (CDCl₃, 75MHz): δ 14.3, CH₃; 38.3, CH₂Ph; 53.6, COCH; 62.0, OCH₂; 82.2, C₆₀sp³; 83.6, C₆₀sp³; 95.4, ΨPh₂; (127.4, 128.4, 128.5, 128.53, 128.6, 128.8, 129.7, 129.8, 129.83, 130.2, 132.5) ArC's; (134.8, 134.9, 135.7 (2 x C), 136.7, 136.8) C₆₀sp³'s; 137.7, CH₂ArC₁; (139.2, 139.3, 139.6, 139.64, 140.9, 141.2) C₆₀sp³'s; 141.4, CArC₁,1' (NB the qC are not equivalent); (141.78, 141.8, 141.9, 142.0, 142.04, 142.1, 142.5, 142.53, 142.7 (2 x C), 142.8, 142.85, 142.87, 142.9, 143.1, 144.2 (2 x C), 144.5, 144.97, 145.0, 145.2 (2 x C), 145.3, 145.4, 145.5, 145.56, 145.6, 145.62, 145.64 (2 x C), 145.9, 145.95, 146.0, 146.05, 146.1, 146.13, 146.49, 146.5, 147.0, 147.2, 148.5, 148.7, 149.1, 149.14, 153.2, 153.3) C₆₀sp³'s; 160.7, NHCO; 161.8, CN; 170.9, CO. ESI-MS (+ve): m/z 1133 (100%, M+H).

**Ethyl N-acetyl-α-(1,9-dihydrofullereny1)glycinate 118**

To a solution of the free amine 111a (freshly prepared from 99a (0.10 mmol)) in CH₂Cl₂ (50 mL) was added MgSO₄ (0.18 g, 1.5 mmol), acetic anhydride (0.050 g, 0.50 mmol) and NaHCO₃ (0.084 g, 1.0 mmol) and the mixture was stirred at RT for 6 h. The solution was then washed with water, dried (MgSO₄) and evaporated *in vacuo*. The crude material was then subjected to silica gel column chromatography. Elution with CH₂Cl₂ provided the title compound 118 (0.041 g, 47%,
over 2 steps from 99a) as a brown solid. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.41, t, 3H, $J = 6.5$ Hz, CH$_2$CH$_3$; 2.39, s, 3H, COCH$_3$; 4.49, m, 2H, CH$_2$; 6.63, d, 1H, $J = 9.5$ Hz, CH; 6.92, s, 1H, C$_{60}$H; 7.21, d, 1H, $J = 9.5$ Hz, NH. $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 14.6, CH$_2$CH$_3$; 23.9, COCH$_3$; 57.8, C$_{60}$sp$^3$H; 62.4, CH; 63.0, CH$_2$CH$_3$; 67.9, C$_{60}$sp$^3$CH; 136.1, 136.2, 136.6, 137.3, 139.8, 139.9, 140.65, 140.7, 141.6, 141.7, 141.75, 141.8, 141.85, 141.9, 142.2, 142.25, 142.3 (2 x C), 142.45, 142.5, 142.8, 142.85, 142.9 (2 x C), 143.4, 143.45, 144.55, 144.6, 144.9, 144.95, 145.5, 145.6 (2 x C), 145.65, 145.65, 145.7, 145.8, 145.85, 145.9, 145.95, 146.2, 146.4 (2 x C), 146.45, 146.5, 146.6 (2 x C), 146.65, 146.7 (2 x C), 147.0, 147.1, 147.5, 147.8, 150.6, 151.3, 153.1, 153.5) C$_{60}$sp$^2$; 170.1, CO$_2$Et; 171.2, COMe. ESI-MS (+ve): $m/z$ 866 (100%, M+H).

**Ethyl 5-spirocyclohexylfulleropyrrolidine-2-carboxylate 119**

To a solution of the free amine 111a (freshly prepared from 99a (0.10 mmol)) in CH$_2$Cl$_2$ (50 mL) was added MgSO$_4$ (0.18 g, 1.5 mmol), cyclohexanone (0.020 g, 0.20 mmol) and NaHCO$_3$ (0.084 g, 1.0 mmol) and the mixture was stirred at RT for 10 h. The reaction was then concentrated in vacuo and subjected to silica gel chromatography, elution with CH$_2$Cl$_2$ afforded the title compound 120 (0.038 g, 42% over 2 steps from 99a) as a brown solid. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.28, t, 3H, $J = 7.2$ Hz, CH$_3$; 1.90, m, 5H, cyclohexyl; 2.20, m, 3H, cyclohexyl; 2.28, m, 2H, cyclohexyl; 2.59, dt, 1H, $J = 4.2$, 13.5 Hz, cyclohexyl; 2.95, m, 1H, cyclohexyl; 4.29, m, 1H, CHHCH$_3$; 4.43, m, 1H, CHHCH$_3$; 5.63, s, 1H, CHCO$_2$. $^{13}$C NMR (CDCl$_3$/CS$_2$, 150 MHz): $\delta$ 14.3, CH$_3$; 23.2, C$_5$; 24.2, C$_3$; 26.2, C$_4$; 37.0, C$_6$; 38.3, C$_2$; 61.6, CH$_2$CH$_3$; 71.7, CHCO$_2$; 74.4, C$_1$; 77.9, C$_{60}$sp$^3$CHCO$_2$; 83.2, C$_{60}$sp$^3$C$_1$; (135.0, 135.3, 135.9, 136.3, 139.1, 139.4, 139.5, 139.7, 141.3, 141.35, 141.5, 141.6, 141.7, 141.8,
141.85, 141.9, 141.95, 142.0, 142.1, 142.2, 142.3, 142.35, 142.4, 142.5, 142.8, 142.85, 142.9, 143.9, 144.0, 144.1, 144.2, 144.6, 144.8, 144.85, 144.9, 144.93, 144.98, 145.0, 145.05, 145.1, 145.2, 145.3, 145.4, 145.5, 145.55, 145.6, 145.7, 145.8, 145.9, 145.95, 146.0, 146.6, 146.65, 146.7, 151.1, 153.1, 153.5, 154.0) C_{60}sp^2; 169.2, CO. ESI-MS (+ve): 904 (100%, M+H).

Ethyl (5,5-dimethylfulleropyrrolidine)-2-carboxylate 120

To a solution of the free amine 111a (freshly prepared from 99a (0.10 mmol)) in CH₂Cl₂ (50 mL) was added MgSO₄ (0.18 g, 1.5 mmol), acetone (0.020 g, 0.35 mmol) and NaHCO₃ (0.084 g, 1.0 mmol) and the mixture was stirred at RT for 10 h. The reaction was then concentrated in vacuo and subjected to silica gel chromatography, elution with CH₂Cl₂/hexanes (7 : 3) afforded the title compound 120 (0.042 g, 48% over 2 steps from 99a) as a brown solid. The spectral data was identical to that reported.\(^{132}\) \(^1\)H NMR (CDCl₃, 500 MHz): δ 1.28, t, 3H, J = 7.0 Hz, CH₂CH₃; 2.14, s, 3H, CH₃; 2.16, s, 3H, CH₃; 4.23, m, 1H, CHHCH₃; 4.38, m, 1H, CHHCH₃; 5.64, s, 1H, CH. \(^{13}\)C NMR (CDCl₃, CS₂ (3 : 2), 125 MHz): δ 14.4, CH₂CH₃; 28.2, CH₃; 29.4, CH₃; 61.9, CH₂; 70.6, C(CH₃)₂; 72.1, CH; 76.5, C_{60}sp^3; 78.2, C_{60}sp^3; (135.1, 135.4, 136.1, 139.3, 139.6, 139.8, 140.0, 141.5, 141.6, 141.7, 141.9, 149.94 (3 x C), 142.1, 142.18 (2 x C), 142.2, 142.2, 142.5 (2 x C), 142.6, 142.7, 143.0, 143.1, 144.1, 144.2, 144.3, 144.4, 144.9, 145.0, 145.13, 145.15, 145.16, 145.17, 145.19, 145.2, 145.21, 145.3, 145.5, 145.6, 145.75, 145.8 (2 x C), 145.9, 146.0, 146.14, 146.16, 146.2, 146.7, 146.9, 147.0, 151.3, 153.4, 153.3, 154.0) C_{60}sp^2; 169.2, C=O. ESI-MS (+ve): 864 (100%, M+H).
cis-Ethyl (5-tert-butylfulleropyrrolidine)-2-carboxylate 121

**Method 1**

DBU (0.073 g, 0.48 mmol) was added at RT to a solution containing [60]fullerene (0.086 g, 0.12 mmol) and ethyl N-(tert-butylmethylene)imino glycinate (138) (0.024 g, 0.14 mmol) in chlorobenzene (50 mL). The solution was stirred at RT overnight then subjected to flash silica gel chromatography, elution with CH$_2$Cl$_2$/hexanes (1 : 1) provided the title compound 121 as a fine black solid (0.068 g, 64%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.24, t, 3H, $J = 7.0$ Hz, CH$_2$CH$_3$; 1.58, m, 9H, CH$_3$; 3.72, t, 1H, $J = 14.0$ Hz, NH; 4.33, m, 2H, CH$_2$CH$_3$; 4.59, d, 1H, $J = 14.0$ Hz, CHC(CH$_3$)$_3$; 5.42, d, 1H, $J = 14.0$ Hz, CHCO$_2$). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 14.3, CH$_2$CH$_3$; 29.7, (CH$_3$)$_3$; 36.1, C(CH$_3$)$_3$; 62.0, CH$_2$CH$_3$; 73.2, CHC(CH$_3$)$_3$; 78.8, C$_{60}$sp$^3$CHC(CH$_3$)$_3$; 79.8, C$_{60}$sp$^3$CHCO$_2$; 83.2, CHCO$_2$; (135.3, 135.5, 136.3, 136.7, 138.9, 139.1, 139.5, 139.7; 141.4, 141.6, 141.76, 141.8, 142.0, 142.1, 142.2, 142.3 (2 x C), 142.32, 142.4, 142.5; 142.7, 142.71, 142.74, 142.8, 143.0, 143.3, 144.2, 144.3, 144.4, 144.5, 145.1, 145.1; 145.17 (2 x C); 145.2, 145.27; 145.3 (2 x C); 145.5; 145.6; 145.7; 145.86 (2 x C); 145.9; 146.0, 146.1, 146.2, 146.24, 146.3, 146.33, 146.9 (2 x C); 147.0, 151.0, 152.5, 154.3, 154.4) C$_{60}$sp$^2$; 169.8, CO$_2$. ESI-MS (-ve): $m/z$ 891 (100%, M$^-$).

**Method 2**

To a solution of [60]fullerene (0.086 g, 0.12 mmol) in chlorobenzene (60 mL) was added, ethyl N-(2,2-dimethylpropylidene)glycinate (138) (0.041 g, 0.24 mmol) and manganese(III) acetate dihydrate (0.064 g, 0.24 mmol). The reaction mixture was then heated at reflux under an atmosphere of nitrogen for 2 h. The crude mixture was then applied directly to a flash silica gel column, elution with a CH$_2$Cl$_2$/hexanes (1 : 1)
afforded 121 as a fine black powder (0.041 g, 38%). Which was spectroscopically identical that reported for method 1.

Method 3

To a solution of pyrrole 148 (0.027 g, 0.030 mmol) in CH₂Cl₂ (40 mL) at 0 °C under an atmosphere of nitrogen was added dropwise boron trifluoride-diethyl etherate (0.043 g, 0.30 mmol) over 1 min. The reaction mixture was stirred for 15 min then THF (20 mL) and sodium cyanoborohydride (0.019 g, 0.30 mmol) were added and the solution was stirred for 30 min. The reaction was then concentrated in vacuo, the residue redissolved in CH₂Cl₂ (40 mL) and washed with a saturated NH₄Cl solution (10 mL). The organic phase was collected, dried (MgSO₄), filtered and concentrated under reduced pressure to approximately half the volume. The crude material was then subjected to silica gel column chromatography, elution with toluene/hexanes (1 : 1) yielded 121 (0.020 g, 76%) as a brown amorphous solid. Which was spectroscopically identical that reported for method 1.

N-Phthaloylglycine¹⁵⁵

![N-Phthaloylglycine structure](image)

To a suspension of glycine (1.0 g, 13 mmol) and phthalic anhydride (1.9 g, 13 mmol) in toluene (50 mL) was added Et₃N (1.5 g, 15 mmol). The mixture was then vigorously heated at reflux under azeotropic conditions for 3 h before the cooled solution was concentrated in vacuo, redissolved in ethyl acetate (100 mL) and washed with brine (3 x 50 mL). The organic phase was then collected, dried (MgSO₄) and concentrated under reduced pressure to provide the title compound (0.78 g, 29%) as a crystalline white solid. ¹H NMR (CD₃COCD₃, 300 MHz): δ 4.52, s, 2H, CH₂; 7.96, m, 4H, 4 x ArH; 10.81, bs, 1H, OH. ¹³C NMR (CDCl₃, 75 MHz) δ 39.1, CH₂; 124.0, ArC3,6; 132.8, ArC1,2; 135.3,
Chapter 7: Experimental

ArC₄,5; 167.5, CO₂; 168.6, CO. ESI-MS (-ve): m/z 204 (100%, M-H). This compound, which is commercially available, was previously characterised by m.p., and to the best of our knowledge no NMR data has been reported. m.p. 186-188 °C lit. 191-192 °C.¹⁵⁵

*N*-Phthaloylglycyl chloride¹³⁴

To a suspension of phthlimide glycinate (0.50 g, 2.4 mmol) in toluene (20 mL) was added freshly distilled thionyl chloride (2.0 g, 17 mmol) and the mixture was stirred at reflux for 1 h. The cooled solution was then reduced *in vacuo* providing the title compound (0.54 g, 100%) as an off-white solid. ¹H NMR (CDCl₃, 300 MHz): δ 4.83, s, 2H, CH₂; 7.79, dd, 2H, J = 3.5, 6.0 Hz, ArH₄,₅; 7.91, dd, 2H, J = 3.5, 6.0 Hz, ArH₃,₆. The spectral data of this commercially available compound was identical to that reported.¹³⁴

**Ethyl N-(*N*-phthaloylglycyl)-α-(1,9-dihydrofullerenyl) glycinate 123**

To a solution of the fullerene amino ester 111a (freshly prepared from 99a (0.10 mmol)) in CH₂Cl₂ (50 mL) was added MgSO₄ (0.18 g, 1.5 mmol), phthylglycine chloride (0.045 g, 0.20 mmol) and NaHCO₃ (0.084 g, 1.0 mmol) and the solution was stirred at RT for 16 h. The solution was washed with water (3 x 50 mL), dried (MgSO₄), filtered and evaporated *in vacuo.*

The crude residue was then subjected to flash silica gel chromatography. Elution with CH₂Cl₂/hexanes (7 : 3) provided the title compound 123 (0.038 g, 29%, over 2 steps from 99a) as a brown solid. ¹H NMR (CDCl₃, 500 MHz): δ 1.44, t, 3H, J = 7.0 Hz, CH₃; 4.54, q, 2H, J = 7.0 Hz, CH₂CH₃; 4.71, ABq, J = 16.0 Hz, 2H, NCH₂; 6.58, d, 1H, J = 9.5 Hz, CH; 6.86, s, 1H,
C<sub>60</sub>H; 7.72, dd, 2H, J = 5.5, 3.5 Hz, ArH<sub>4</sub>, 5; 7.77, d, 1H, J = 9.5 Hz, NH; 7.88, dd, 2H, 
J = 5.5, 3.5 Hz, ArH<sub>3</sub>.<sub>6</sub>.<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 14.6, CH<sub>3</sub>; 41.6, NCH<sub>2</sub>; 57.5, 
C<sub>60</sub>sp<sup>3</sup>H; 62.3, CHNH; 63.3, OCH<sub>2</sub>; 67.8, C<sub>60</sub>sp<sup>3</sup>; 124.0, ArC<sub>3</sub>, 6; 132.1, ArC<sub>1</sub>, 2; 
134.6, ArC<sub>4</sub>, 5; (135.9, 136.1, 136.6, 137.2, 139.8, 139.9, 140.6 (2 x C), 141.5, 141.6, 
141.66, 141.72, 141.8, 141.9, 142.18, 142.19, 142.25, 142.26, 142.35, 142.4, 142.7 (2 x 
C), 142.8, 143.2, 143.3, 143.33, 144.53, 144.54, 144.85, 144.86, 145.46 (2 x C), 145.53, 
145.54, 145.64, 145.65, 145.79, 145.82, 145.83, 145.9, 146.0, 146.37, 146.38, 146.39, 
146.40, 146.43, 146.5 (2 x C), 146.6 (2 x C), 146.9, 147.0, 147.5, 147.8, 150.3, 150.9, 
152.9, 153.2) C<sub>60</sub>sp<sup>2</sup>; 167.5, NHCO; 167.8, NCO; 169.5, CO<sub>2</sub>Et. ESI-MS (+ve): m/z 
1033 (100%, M+Na).

**N-Phthaloylglycylglycinoyl chloride 124**

To a suspension of 125 (0.10 g, 0.38 mmol) in oxalyl chloride (5.0 g, 39 mmol) was added 
benzyltriethylammonium chloride (0.0010 g, 4.4 µmol) and DMF (0.010 g, 0.14 mmol) and the solution was stirred at RT for 1 h. The solution was then concentrated, providing the acid chloride (0.11 g, 100%) as a yellow solid, which was used immediately in subsequent reactions.

**N-Phthaloylglycylglycine 125**

To a test tube containing GlyGly (0.10 g, 0.76 mmol) was added phthalic anhydride (0.56 g, 3.8 mmol) and the mixture heated at 200 °C for 1 h, before being allowed to cool to RT. The mixture was then washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), then methanol (3 x 10 mL), providing the title compound (0.15 g, 74%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD,
500 MHz): δ 3.93, s, 2H, NHCH₂; 4.42, s, 2H, NCH₂; 7.83, dd, 2H, J = 3.0, 5.5 Hz, ArH; 7.89, dd, 2H, J = 3.0, 5.5 Hz, ArH. ¹³C NMR (CD₃OD, 125 MHz): δ 40.9, CH₂CO₂; 41.9, CH₂CON; 124.3, ArC, 133.5, ArC; 135.5, ArC; 168.7, CON; 169.1, CONH; 173.6, CO. ESI-MS (+ve): m/z 263 (100%, M+H). m.p.- 223-5 °C, lit.- 228 °C. ¹³⁵ This compound was previously characterised by m.p., and to the best of our knowledge no NMR data has been reported.

Methyl N-phthaloylglycylglycinate 126

To a solution of 124 (0.11 g, 0.38 mmol) in anhydrous methanol (5 mL, 0.12 mol) was added pyridine (0.010 g, 0.13 mmol) and the reaction mixture was stirred at RT for 1 h before being reduced in vacuo. The crude residue was then dissolved in CH₂Cl₂ (20 mL) and washed with saturated Na₂CO₃ (3 x 10 mL), the organic phase was collected, dried (MgSO₄), filtered and concentrated to provide the title compound 126 (0.098 g, 93%) as a white solid, which was spectroscopically equivalent to that reported in the literature.¹³⁶ ¹H NMR (CDCl₃, 500 MHz): δ 3.64, s, 3H, CH₃; 4.04, s, 2H, NHCH₂; 4.34, s, 2H, NCH₂; 7.73, m, 4H, ArH. ¹³C NMR (125 MHz): δ 40.1, NHCH₂; 51.6, NCH₂; 52.8, CH₃; 122.7, ArC₃, 6; 131.0, ArC1,2; 133.7, ArC4,5; 166.6, CO; 167.0, CO; 169.4, CO, ESI-MS (+ve): m/z 277 (100%, M+H).
Chapter 7: Experimental

\(N_\alpha^{\text{-Fmoc}}-N_\varepsilon^{\text{-Boc}}-\text{L-Lysinoyl chloride} \ 128^{138}\)

A solution of \(N_\alpha^{\text{-Fmoc}}-N_\varepsilon^{\text{-Boc}}-\text{L-Lysine} \) (0.10 g, 0.22 mmol) and \(\text{Na}_2\text{CO}_3 \) (0.10 g, 0.94 mmol) in \(\text{CH}_2\text{Cl}_2 \) (5 mL) was treated with thionyl chloride (2.0 g, 16 mmol) and the reaction sonicated for 30 min. The solvent was removed under reduced pressure to provide the acid chloride \(128 \) (0.10 g, 96%) as a white solid, which was used immediately in the next reaction without further purification.

\textit{Ethyl N-(N_\alpha'-^{\text{-Fmoc}}-N_\varepsilon'-^{\text{-Boc}}-\text{L-Lysinoyl})-\alpha-(1,9-di}h\text{ydro}f\text{ullerenyl) glycinate} \ 129.\)

To a solution of the fullerenyl amino ester \(111\text{a} \) (freshly prepared from \(99\text{a} \) (0.10 mmol)) in \(\text{CH}_2\text{Cl}_2 \) (50 mL) was added \(\text{MgSO}_4 \) (0.18 g, 1.5 mmol), \(128 \) (0.20 g, 0.40 mmol) and \(\text{NaHCO}_3 \) (0.084 g, 1.0 mmol) and the solution was stirred at RT for 16 h. The solution was washed with water (3 x 50 mL), dried (\(\text{MgSO}_4 \)), filtered and evaporated \textit{in vacuo}. The crude residue was then subjected to flash silica gel chromatography. Elution with \(\text{CH}_2\text{Cl}_2 \) provided the title compound \(129 \) (0.014 g, 11%, over 2 steps from \(99\text{a} \)) as a 1 : 1 mixture of diastereomers. The sample was contaminated with \(N_\alpha^{\text{-Fmoc}}-N_\varepsilon^{\text{-Boc}}-\text{L-Lysine} \) (∼60% as determined by \(^1\text{H NMR})\), which made assignment of all NMR peaks difficult. Therefore only the clearly resolved peaks (attributable to either or both diastereomers of \(129 \)) are reported. \(^1\text{H NMR (CDCl}_3, 500 \text{ MHz}): \delta \ 4.24, \text{ q, } 2\text{H, } J = 6.5 \text{ Hz, CH}_2\text{CH}_3;\)
6.55, s, 1H, H₆; 6.57, s, 1H, H₆; 6.86, s, 1H, C₆H; 6.88, s, 1H, C₆H; 8.14, bs, 2H, NH; 8.17, bs, 4H, NH. ¹³C NMR (125 MHz): δ 14.3, CH₂CH₃; 14.5, CH₂CH₃; 21.1, NHCH₂CH₂CH₂; 21.8, NHCH₂CH₂CH₂; 39.6, NHCH₂; 47.1, C₆; 52.6, C₆; 60.5, C₆sp³H; 62.2, C₆; 62.99, CH₂CH₃; 63.0, CH₂CH₃; 67.6, C₆sp³; 67.8, C₆sp³; 83.3, C(CH₃)₃; 127.4, ArC; 128.8, ArC; (136.6, 137.25, 137.26, 139.6, 139.8, 141.6, 141.8) C₆sp²; 142.1, ArC; (142.25, 142.26, 142.7, 142.71, 142.73, 143.2, 143.3) C₆sp²; 143.8, ArC; 143.9, ArC; (144.5 (2 x C), 144.7 (2 x C), 145.4, 145.5 (2 x C), 145.6 (2 x C), 145.8 (2 x C), 146.2, 146.5, 146.6, 146.7, 146.8, 147.4 (2 x C), 147.7, 153.3) C₆sp²; 156.2, CO; 156.3, CO; 169.6, CO₂Et. ESI-MS (+ve): m/z 1274 (M+H)⁺, (10%), m/z 1296 (100%, M+Na)⁺.

**Methyl N-BocGlycylphenylalaninate 134**

A solution of *N*-tert-butoxycarbonylglycine (1.0 g, 5.7 mmol), EDCI (1.5 g, 8.0 mmol) and HOBt (1.1 g, 8.0 mmol) in CH₂Cl₂ (20 mL) was stirred at RT for 15 min before methyl L-phenylalaninate hydrochloride (1.2 g, 5.7 mmol) and Et₃N (1.2 g, 12 mmol) was added and the solution stirred for 20 h under an atmosphere of nitrogen. Additional CH₂Cl₂ (30 mL) was added and the mixture was washed with water (50 mL) then brine (50 mL). The organic phase was then collected, dried (MgSO₄), and filtered before being reduced in vacuo. The crude mixture was then subjected to flash silica gel chromatography, elution with CH₂Cl₂ provided the title compound 134 (1.2 g, 63%) as a pale yellow oil, which was spectroscopically identical to that reported in the literature (Only ¹H NMR reported).¹³⁹ ¹H NMR (CDCl₃, 300 MHz): δ 1.35, s, 9H, (CH₃)₃; 3.00, m, 2H, CH₂Ph; 3.57, s, 3H, OCH₃; 3.66, t, 2H, J = 6.0 Hz, CH₂NH; 4.76, m, 2H, CH; 5.65, t, 1H, J = 6.0 Hz, NHCH₂; 7.03, m, 2H, NH, ArH; 7.16, m, 4H, ArH. ¹³C NMR
(CDCl$_3$, 75 MHz): $\delta$ 28.0, (CH$_3$)$_3$; 37.6, CH$_2$Ph; 43.7, NHCH$_2$; 52.0, OCH$_3$; 53.0, CH; 79.5, C(CH$_3$)$_3$; 126.8, ArC4; 128.3, ArC3,5; 129.0, ArC2,6; 135.7, ArCl; 155.9, CO$_2$ C(CH$_3$)$_3$; 169.4, CONH; 171.7, CO$_2$Me. ESI-MS (+ve): $m/z$ 337 (100%, M+H).

Methyl Glycylphenylalaninate trifluoroacetate salt 135

To a solution of 134 (1.2 g, 3.6 mmol) in CH$_2$Cl$_2$ (2 mL) was added TFA (5 mL) and the solution stirred rigorously for 1 h before the solvent was reduced in vacuo providing the crude salt (1.2 g, 94%) as a yellow oil, which was essentially pure from $^1$H NMR analysis and could be used in the next reaction without further purification. To the best of our knowledge no data (spectral or otherwise) has been reported for this compound.

$^1$H NMR (CD$_3$OD, 300 MHz): $\delta$ 2.98, dd, 1H, $J = $ Hz, CH$_2$Ph; 3.14, dd, 1H, $J = $ Hz, CH$_2$Ph; 3.64, s, 3H, CH$_3$; 3.74, q, 2H, $J = $ 15 Hz, CH$_2$NH$_3$; 4.75, m, 1H, CH; 6.48, bs, 3H, NH$_3$; 7.20, m, 5H, ArH; 8.18, bs, 1H, NH. $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 39.1, CH$_2$Ph; 42.3, CH; 53.7, CH$_3$; 56.2, COCH$_2$; 117.7, q, $J = $ 286.5 Hz, CF$_3$; 128.8, ArC4; 130.3, ArC3,5; 130.9, ArC2,6; 138.2, ArCl; 162.4, q, $J = $ 38.3 Hz, CF$_3$CO; 168.3, NHCO; 173.9, CO$_2$. ESI-MS (+ve): $m/z$ 351 (100%, M+H).

Methyl N-(diphenylmethylene)glycylphenylalaninate 136

To a suspension of 135 (1.0 g, 2.9 mmol) in CH$_2$Cl$_2$ (10 mL) was added benzophenone imine (0.52 g, 2.9 mmol) and the reaction mixture was stirred vigorously for 24 h then filtered and concentrated under reduced pressure. The crude residue was then redissolved in diethyl ether (20 mL) and washed with brine (3 x 20 mL). The organic phase was then dried (MgSO$_4$), filtered and concentrated to provide the protected
dipeptide 136 (0.44 g, 38%) as a white solid. To the best of our knowledge no data (spectral or otherwise) has been reported for this compound. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.21, m, 2H, CH$_2$Ph; 3.73, s, 3H, OCH$_3$; 3.96, s, 2H, NCH$_2$; 5.01, m, 1H, CH; 6.73, bd, $J$ = 8.5 Hz, 1H, NH, 7.08, m, 3H, ArH; 7.28, m, 3H, ArH; 7.32, m, 2H, ArH; 7.48, m, 5H, ArH; 7.61, m, 2H, ArH. $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 38.0, CH$_2$Ph; 52.2, CH; 52.6, CH$_3$; 56.4, CH$_2$; (127.1, 127.2, 128.2, 128.5, 128.7, 128.8, 129.0, 129.3, 130.7, 135.9, 138.6) ArC’s; 170.2, 170.4, 171.8. ESI-MS (+ve): m/z 401 (100%, M+H).

Ethyl-N-(2,2-dimethylpropylidene)glycinate 138

To a suspension of ethyl glycinate hydrochloride (0.28 g, 2.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added Et$_3$N (0.20 g, 2.0 mmol) at RT. The mixture was stirred for 10 min before MgSO$_4$ (0.36 g, 3.0 mmol) and pivaldehyde (0.17 g, 2.0 mmol) was added and the mixture was stirred for a further 30 min. The suspension was filtered and the solution reduced in vacuo then redissolved in diethyl ether, washed with water (3 x 10 mL), dried (MgSO$_4$), filtered and concentrated to provide the title compound (0.28 g, 82%) as a colourless oil. The spectral data was spectroscopically equivalent to that reported.$^{43}$ $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 1.01, s, 9H, (CH$_3$)$_3$; 1.20, t, $J$ = 7.0 Hz, 3H, CH$_2$CH$_3$; 4.07, d, $J$ = 1.2 Hz, 2H, NCH$_2$; 4.12, q, $J$ = 7.0 Hz, 2H, CH$_2$CH$_3$; 7.44, t, $J$ = 1.2 Hz, 1H, CH=N. $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 14.0, CH$_2$CH$_3$; 26.6, (CH$_3$)$_3$; 36.4, C(CH$_3$)$_3$; 60.7, CH$_2$CH$_3$; 61.5, NCH$_2$; 170.1, CO; 176.9, CH=N. ESI-MS (+ve): m/z 172 (100%, M+H).

Ethyl 2-(2,2’,4,4’-tetramethylpentan-3-ylidene)glycinate 139

To a solution of ethyl bromoacetate (0.19 g, 1.3 mmol) and 2,2’,4,4’-tetramethyl-3-pentanone imine (0.16 g, 1.3 mmol) in
acetonitrile (5 mL) in a pressure vessel was added anhydrous sodium carbonate (0.14 g, 1.3 mmol) which was stirred at 130 °C for 3 days. The reaction mixture was then filtered and reduced in vacuo, redissolved in chloroform (10 mL) and washed with water (2 x 10 mL) and then brine (2 x 10 mL). The organic phase was then collected, dried (MgSO₄), filtered and concentrated to provide the title compound (0.21 g, 73%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.22, s, 9H, trans-(CH₃)₃; 1.27, t, 3H, J = 7.3 Hz, CH₂CH₃; 1.31, s, 9H, cis-(CH₃)₃; 4.19, q, 2H, J = 7.3 Hz, CH₂CH₃; 4.48, s, 2H, NCH₂. ¹³C NMR (CDCl₃, 75 MHz) δ 14.2, CH₂CH₃; 30.1, trans-(CH₃)₃; 30.8, cis-(CH₃)₃; 40.4, trans-C(CH₃)₃; 44.0, cis-C(CH₃)₃; 54.4, NCH₂; 60.5, CH₂CH₃; 171.4, CO; 181.5, CN. ESI-MS (+ve): m/z 228 (100%, M+H). HR ESI-MS (+ve): m/z calculated for (M+H) C₁₃H₂₆NO₂: 228.1964, found 228.1968.

tert-Butyl N-[(1R, 4R)-bornylidene]glycinate 140b

To a solution of tert-butyl glycinate (0.39 g, 3.0 mmol) in toluene (10 mL) was added thiocamphor (0.50 g, 3.0 mmol). The solution was then heated at reflux for 36 h before the solution was cooled to RT and concentrated in vacuo with the crude residue purified via silica gel column chromatography. Elution with ethyl acetate/hexanes (3 : 10) provided the title compound 140b (0.676 g, 85%) as a colourless oil, which was spectroscopically identical to that reported in the literature. ¹H NMR (CDCl₃, 300MHz): δ 0.70, s, 3H; 0.85, s, 3H; 0.92, s, 3H; 1.37, s, 9H; 1.55-1.90, m, 6H; 2.21, m, 1H; 3.91, ABq, 2H, J = 16 Hz. ESI-MS (+ve): m/z 266 (100%, M+H).
Chapter 7: Experimental

Ethyl N-[bis(methylthio)methylene]glycinate 143 and N-[(thiomethyl)thioxomethyleneamine]ethyl ester 145

To a solution of glycine ethyl ester hydrochloride (1.0 g, 7.2 mmol) in anhydrous CH₂Cl₂ (50 mL) was added CS₂ (0.55 mL, 9.1 mmol) and Et₃N (2.1 mL, 15 mmol), which was stirred for 1 h at RT. MeI in aliquots (5 x (0.1 mL, 1.4 mmol)) was then added every 10 min whilst the solution was heated at reflux. After 1 h the solution was washed (H₂O) and concentrated under reduced pressure then re-dissolved in anhydrous acetone (50 mL). To the solution was added DBU (1.1 g, 7.2 mmol) and the reaction mixture was heated at reflux for 2 h with the addition of MeI in aliquots (10 x (0.1 mL, 1.4 mmol)) every 10 min. The solution was then washed with water (5 x 50 mL), dried (MgSO₄), filtered and reduced in vacuo before being subjected to flash silica gel chromatography. Elution with diethyl ether/hexanes (1 : 4) provided the title compound 143 (0.94 g, 63%) as a yellow oil. The spectral data was identical to that reported.¹⁴⁷ ¹H NMR (CDCl₃, 300 MHz): δ 1.30, t, J = 7.0 Hz, 3H, CH₂CH₃; 2.45, s, 3H, trans-SCH₃; 2.58, s, 3H, cis-SCH₃; 4.22, q, J = 7.0 Hz, 2H, CH₂CH₃; 4.23, s, 2H, COCH₂N. ¹³C NMR (CDCl₃, 75 MHz): δ 14.17, CH₂CH₃; 14.60, trans-SCH₃; 14.87, cis-SCH₃; 54.19, COCH₂N; 60.89, CH₂CH₃; 163.21, C=N; 170.28, CO. ESI-MS (+ve): m/z 208 (100%, M+H).

Further elution with diethyl ether/hexanes (4 : 1) provided 145 as a yellow oil (0.22 g, 18%). The spectral data was identical to that reported.¹⁴⁷ ¹H NMR (CDCl₃, 300 MHz): 1.83, t, 3H, J = 7.0 Hz, CH₂CH₃; 2.50, s, 3H, SCH₃; 4.13, q, 2H, J = 7.0 Hz, CH₂CH₃; 4.34, d, 2H, J = Hz, CH₂NH. ¹³C NMR (CDCl₃, 75 MHz): δ 13.57, CH₂CH₃; 17.75, CH₂CH₃; 47.58, SCH₃; 61.32, NHCH₂; 168.39, CO; 199.48, CS. ESI-MS (+ve): m/z 174 (100%, M+H).
**tert-Butyl N-[bis(methylthio)methylene]glycinate**

To tert-butyl glycinate hydrochloride (1.0 g, 6.0 mmol) was added, precooled (0 °C) solutions of NaOH (3.6 g, 90 mmol) in water (5 mL), and carbon disulfide (0.37 mL, 6.0 mmol) in benzene (15 mL). Methyl iodide (1.2 mL, 20 mmol) and benzyltriethylammonium chloride (0.10 g, 0.44 mmol) were then added. The mixture was vigorously stirred at RT for 30 min. The benzene phase was decanted and the water phase extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine (3 x 15 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude residue was then subjected to column chromatography. Elution with ethyl acetate/hexanes (3 : 2) afforded the title compound (1.1 g, 78%) as a colourless oil. The spectral data was identical to that reported.¹⁴⁸ ¹H NMR (CDCl₃, 500MHz): δ 1.49, s, 9H, (CH₃); 2.45, s, 3H, trans-SCH₃; 2.56, s, 3H, cis-SCH₃; 4.15, s, 2H, CH₂. ¹³C NMR (CDCl₃, 75 MHz): δ 14.52, trans-SCH₃; 14.83, cis-SCH₃; 28.02, (CH₃)₅; 54.81, CH₂; 81.04, CCH₃; 162.55, C=N; 169.26, CO. ESI-MS (+ve): m/z 236 (100%, M+H).

**tert-Butyl 61-(dithiomethylmethylideneamino)methanofullerene-61-carboxylate**

DBU (0.085 mL, 0.56 mmol) was added at RT to a solution containing [60]fullerene (0.10 g, 0.14 mmol), carbon tetrabromide (0.060 g, 0.18 mmol) and N-[bis(thiomethyl)methyleneamine]tert-butyl ester (0.042 g, 0.18 mmol) in anhydrous toluene (100 mL) under a atmosphere of anhydrous argon. The solution was stirred for 18 h then subjected to flash silica gel chromatography eluting with CH₂Cl₂/hexanes (1 : 1) to remove the unreacted [60]fullerene and polymeric material. The second column was performed using 2 : 3
CH$_2$Cl$_2$/hexanes to deliver a brown solid (0.0080 g, 6%) tentatively assigned as the title compound. $^1$H NMR (CDCl$_3$, 300MHz): δ 1.24, s, 9H, C(CH$_3$)$_3$; 2.72, s, 3H, SCH$_3$; 2.80, s, 3H, SCH$_3$.

*Ethyl 2,6-dithiocyclohexyliminoglycinate* 144

To a solution of glycine ethyl ester hydrochloride (0.50 g, 3.6 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) was added CS$_2$ (0.27 g, 3.6 mmol) and Et$_3$N (1.0 mL, 7.3 mmol), which was stirred for 1 h at RT, the solution was then washed with water, dried (MgSO$_4$) and concentrated under reduced pressure then re-dissolved in anhydrous acetonitrile (20 mL). To the solution was added Et$_3$N (2 mL, 14.5 mmol), and 1,3-dibromopropane (0.73 g, 3.6 mmol), which was then heated at reflux for 4 h. The solution was then washed repeatedly with water (5 x 50 mL), dried (MgSO$_4$) and reduced *in vacuo* before being subjected to neutral alumina chromatography. Elution with diethyl ether/hexanes (7 : 3) afforded the title compound 144 (0.58 g, 73%) as a pale yellow oil. $^1$H NMR (CDCl$_3$, 500MHz): δ 1.26, t, 3H, $J = 7.0$ Hz, CH$_3$; 2.33, m, 2H, SCH$_2$CH$_2$; 3.01, t, 2H, $J = 5.5$ Hz, *trans* SCH$_2$; 3.61, t, 2H, $J = 5.5$ Hz, *cis* SCH$_2$; 4.20, q, 2H, $J = 7.0$ Hz, CH$_2$CH$_3$; 4.79, s, 2H, NCH$_2$. $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 14.0, CH$_3$; 23.1, CH$_2$CH$_2$S; 32.1, *trans* CH$_2$S; 51.9, *cis* CH$_2$S; 56.3, NCH$_2$; 61.5, CH$_2$CH$_3$ 167.3, CO; 193.9, CS. ESI-MS (+ve): m/z 219 (100%, M$^+$*). HR ESI-MS (+ve): m/z calculated for (M$^+$) C$_8$H$_{13}$NO$_2$S$_2$: 219.0388, found 219.0398.

*Ethyl N-benzylidene glycinate* 146

To ethyl glycinate hydrochloride (0.70 g, 5.0 mmol) and sodium carbonate (0.53 g, 5.0 mmol) in water (20 mL) was added benzaldehyde (0.58 g, 5.0 mmol). The reaction mixture was stirred at 40 °C for
30 min then allowed to return to RT and stirred for a further 16 h. The mixture was then extracted with chloroform (2 x 50 mL) and the combined extracts were washed with brine (2 x 50 mL), dried (MgSO₄), filtered and concentrated \textit{in vacuo} to yield title compound (0.94 g, 98%) as a light orange oil. The spectral data was identical to that reported.\textsuperscript{143} \textsuperscript{1}H NMR (CDCl₃, 300 MHz): \(\delta\) 1.26, t, 3H, \(J = 7.0\) Hz, CH₂CH₃; 4.20, q, 2H, \(J = 7.1\) Hz, CH₂CH₃; 4.35, s, 2H, NCH₂CO; 7.38, m, 3H, ArH; 7.75, m, 3H, ArH; 8.24, s, 1H, CH=N. \textsuperscript{13}C NMR (CDCl₃, 75 MHz) \(\delta\) 13.96, CH₂CH₃; 60.77, CH₂CH₃; 61.78, NCH₂; 128.24, ArC₂,6; 128.34, ArC₃,5; 130.93, ArC₄; 135.39, ArC₁; 165.12, CH=N; 169.84, CO. ESI-MS (+ve): \(m/z\) 192 (100%, M+H).

\textit{Ethyl 61-(2,2-dimethylpropylideneamino)methanofullerene 61-carboxylate 147}

DBU (0.073 g, 0.48 mmol) was added to a 0 °C solution of [60]fullerene (0.086 g, 0.12 mmol), carbon tetrabromide (0.40 g, 1.2 mmol) and \(N\)-(tert-butylmethylene) ethyl glycinate (0.024 g, 0.14 mmol) in chlorobenzene (50 mL). The solution was stirred for 18 h (at 0 °C) then applied directly to a flash silica gel column. Elution with CH₂Cl₂/hexanes (1 : 1) and subsequent recrystallisation from CH₂Cl₂/hexane provided the title compound \textbf{147} (0.014 g, 13%) as a brown amorphous solid, which contained traces (~15%) of the dihydropyrrole \textbf{148}. \textsuperscript{1}H NMR (CDCl₃, 300 MHz): \(\delta\) 1.30, s, 9H, CH₃; 1.48, t, 3H, \(J = 7.0\) Hz, CH₂CH₃; 4.55, q, 2H, \(J = 7.0\) Hz, CH₂CH₃; 8.43 s, 1H, CH. \textsuperscript{13}C NMR (75 MHz, CDCl₃/CS₂ (4:6)): \(\delta\) 14.3, CH₂CH₃; 26.6, (CH₃); 37.8, C(CH₃); 62.9, CH₂; 67.1, NCCO₂Et; 76.2, C₆₀sp³; (138.1, 138.3, 140.9, 140.95, 141.88, 141.89, 142.02, 142.04, 142.8, 142.83 (1/2 x C), 142.85, 142.9 (2 x C), 143.0, 143.7, 143.8, 144.25, 144.3 (1/2 x C), 144.5 (2 x C), 144.6 (2 x C), 144.97, 145.0, 145.01, 145.03, 145.3 (2 x C), 145.5, 146.0) C₆₀sp²; 164.2, CO; 181.5, CN. (Only
3 of the 4 expected half-intensity (1/2 x C) peaks were observed, it was speculated that a full-intensity resonance was obscuring this peak). ESI-MS (-ve): \( m/z \) 889 (100%, M\(^+\)). Further elution with CH\(_2\)Cl\(_2\)/hexanes (1:1) provided 121 (0.031 g, 29%) as a brown solid.

\textit{Ethyl 5-tert-butylfullerenyldihydropyrrole 2-carboxylate 148}

![Chemical Structure]

DBU (0.055 g, 0.36 mmol) was added to a 50 °C solution of [60]fullerene (0.086 g, 0.12 mmol), carbon tetrabromide (0.20 g, 0.6 mmol) and \( N \)-(tert-butylmethylene) ethyl glycinate (0.024 g, 0.14 mmol) in chlorobenzene (50 mL). The solution was stirred for 6 h (at 50 °C) then applied directly to a flash silica gel column. Elution with CH\(_2\)Cl\(_2\)/hexanes (1:1) then recrystallisation from CH\(_2\)Cl\(_2\)/hexane provided the title compound 148 (0.014 g, 13%) as a brown amorphous solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 1.46, t, 3H, \( J = 6.9 \) Hz, CH\(_2\)CH\(_3\); 1.65, s, 9H, (CH\(_3\))\(_3\); 4.53, q, 2H, \( J = 6.9 \) Hz, CH\(_2\)CH\(_3\); 5.96, s, 1H, Ha. HMBC spectrum shown in Figure 3.4. ESI-MS (-ve): \( m/z \) 889 (100%, M\(^+\)).

\textit{Ethyl 61-(2,2,4,4-tetramethylpentan-3-ylideneamino)methanofullerene-61-carboxylate 152a}

![Chemical Structure]

DBU (0.082 mL, 0.56 mmol) was added at RT to a solution of [60]fullerene (0.10 g, 0.14 mmol), carbon tetrabromide (0.18 g, 0.54 mmol) and ethyl 2-(2,2',4,4'-tetramethylpentan-3-ylideneamino)acetate (0.041 g, 0.18 mmol) in toluene (200 mL) in a flame dried two-necked flask covered in Al foil under an atmosphere of argon. The solution was stirred for 12 h before being quenched with water (100 mL). The organic phase was collected and concentrated \textit{in vacuo} at RT in
the dark. The crude residue was subsequently subjected to flash silica gel chromatography, which was also covered in Al foil. Elution with CH₂Cl₂/hexanes (1:1) provided the unstable compound, tentatively assigned as structure 152a, as a brown amorphous solid (0.015 g, 11%). ¹H NMR (CDCl₃, 300 MHz): δ 1.27, s, 18H, (CH₃)₃; 1.27, t, 3H, J = 7.0 Hz, CH₃; 4.25, q, 2H, J = 7.0 Hz, CH₂.

cis-Ethyl 5-phenylfulleropyrrolidine 2-carboxylate 155a and trans-Ethyl 5-phenylfulleropyrrolidine 2-carboxylate 155b

Method 1

A solution of [60]fullerene (0.086 g, 0.12 mmol) and N-benzylimidene glycinate ethyl ester (0.027 g, 0.14 mmol) in chlorobenzene (80 mL) was treated with DBU (0.064 g, 0.42 mmol), and the solution was stirred at RT for 16 h. The crude mixture was applied directly to a flash silica gel column. Elution with CH₂Cl₂/hexanes (3:2) provided 155a (0.059 g, 54%) as a brown solid, which was spectroscopically equivalent to that reported in the literature.¹H NMR (CDCl₃, 300 MHz): δ 1.29, t, 3H, J = 7.0 Hz, CH₂CH₃; 4.06, t, 1H, J = 10.5 Hz, NH; 4.40, m, 2H, CH₂CH₃; 5.64, d, 1H, J = 10.5 Hz, CHAr; 5.86, d, 1H, J = 10.5 Hz, CHCO; 7.38, d, 1H, J = 7.3 Hz, ArH4; 7.46, t, 2H, J = 7.3 Hz, ArH3,5; 7.79, d, 2H, J = 7.3 Hz, ArH2, ArH6. ESI-MS (-ve): m/z 911 (100%, M⁻).

Further elution with CH₂Cl₂/hexanes (3:2) provided 155b (0.015 g, 14%) as a brown solid which was spectroscopically equivalent to that reported in the literature.¹³⁰ ¹H NMR (CDCl₃, 300 MHz): δ 1.24, t, 3H, J = 7.0 Hz, CH₂CH₃; 3.53, bs, 1H, NH; 4.43, m, 2H, CH₂CH₃; 5.80, s, 1H, CHAr; 6.55, s, 1H, CHCO; 7.35, d, 1H, J = 7.5 Hz, ArH4;
7.42, t, 2H, \( J = 7.5 \) Hz, ArH3,5; 7.86, d, 2H, \( J = 7.5 \) Hz, ArH2,6. ESI-MS (−ve): \( m/z \) 911 (100%, \( M^- \)).

**Method 2**

To a solution of [60]fullerene (0.086 g, 0.12 mmol) in chlorobenzene (60 mL) was added \( N \)-benzylidene glycinate ethyl ester (0.046 g, 0.24 mmol) and manganese(III) acetate dihydrate (0.064 g, 0.24 mmol). The solution was heated at reflux under an atmosphere of nitrogen for 1 h. After cooling the crude mixture was applied directly to a flash silica gel column. Elution with \( \text{CH}_2\text{Cl}_2/\text{hexanes} \) (3 : 2) provided 155a (0.030 g, 27%) as a brown solid. Further elution with \( \text{CH}_2\text{Cl}_2/\text{hexanes} \) (3 : 2) provided 155b (0.015 g, 14%) as a brown solid, both compounds were spectroscopically equivalent to that reported for method 1.

**Method 3**

To a solution of [60]fullerene (0.086 g, 0.12 mmol), \( N \)-benzylidene glycinate ethyl ester (0.027 g, 0.14 mmol) and carbon tetrabromide (0.043 g, 0.13 mmol) in chlorobenzene (100 mL) was added DBU (0.064 g, 0.42 mmol). The solution was stirred under an atmosphere of nitrogen for 16 h. The crude mixture was then subjected to flash silica gel chromatography. Elution with \( \text{CH}_2\text{Cl}_2/\text{hexanes} \) (3 : 2) afforded 155a (0.046 g, 42%) and 155b (0.012 g, 11%). both compounds were spectroscopically equivalent to that reported for method 1.
**Chapter 7: Experimental**

*Ethyl N-(2,2-dimethylpropyl)-α-(1,9-dihydrofullerenyl) glycinate 161*

To a solution of 147 (0.013 g, 0.015 mmol) and 148 (0.013 g, 0.015 mmol) in CH₂Cl₂ (40 mL) at 0 °C under an atmosphere of nitrogen was added dropwise boron trifluoride diethyl etherate (0.043 g, 0.30 mmol) over 1 min. The reaction mixture was stirred for 15 min then THF (20 mL) and sodium cyanoborohydride (0.019 g, 0.30 mmol) were added and the solution was stirred for 30 min. The reaction was then concentrated *in vacuo*, the residue redissolved in CH₂Cl₂ (40 mL) and washed with a saturated NH₄Cl solution (10 mL). The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure to approximately half the volume. The crude material was then subjected to silica gel column chromatography.

Elution with toluene/hexanes (1 : 1) yielded 161 (0.0069 g, 26%) as a brown amorphous solid. ¹H NMR (CDCl₃/CS₂, (6:4), 500 MHz): δ 1.33, t, 3H, J = 7.0 Hz, CH₂CH₃; 1.54, s, 9H, (CH₃)₃; 2.76, d, 1H, J = 9.5 Hz, CHHC(CH₃)₃; 3.03, d, 1H, J = 9.5 Hz, CHHHC(CH₃)₃; 4.39, q, 3H, J = 7.0 Hz, CH₃CH₂; 4.96, d, 1H, J = 9.5 Hz, NHCH; 7.02, s, 1H, C₆₀H. ESI-MS (+ve): m/z 894 (M+H). ¹³C NMR (CDCl₃/CS₂, (3 : 2), 500MHz): δ 14.6, CH₂CH₃; 27.9, (CH₃)₃; 32.3, C(CH₃)₃; 59.4, C₆₀Sp³H; 61.6, CH₂CH₃; 61.65, CH₂NH; 68.4, C₆₀Sp³CH; 74.1, CHNH; (136.4, 136.5, 136.7, 138.1, 139.5, 140.3, 141.4, 141.5 (2 x C), 141.6 (2 x C), 142.0 (3 x C), 142.5, 142.55, 142.6, 143.1, 143.2, 144.5, 144.6, 145.1, 145.2 (2 x C), 145.3, 145.4, 145.45, 145.5 (2 x C), 145.6, 145.7, 146.0 (3 x C), 146.15 (2 x C), 146.3 (2 x C), 146.9, 147.1, (2 x C), 147.2) C₆₀Sp²; 172.2, CO. (due to a poor signal to noise ratio not all fullerenyl sp² carbon resonances were resolved). ESI-MS(+ve): m/z 894 (100%, M+H).

Further elution with toluene/hexanes (3 : 1) provided the fulleropyrrolidine 121 (0.0093 g, 35%).
Chapter 7: Experimental

Ethyl 5-thiomethylfullerenyldihydropyrrole 2-carboxylate 171

To a solution of [60]fullerene (0.086 g, 0.12 mmol) in chlorobenzene (60 mL) was added 143 (0.050 g, 0.24 mmol) and manganese(III) acetate dihydrate (0.064 g, 0.24 mmol). The solution was heated at reflux under an atmosphere of nitrogen for 2 h. The crude mixture was then subjected to flash silica gel chromatography. Elution with a CH$_2$Cl$_2$/hexanes (7 : 3) afforded 171 (0.032 g, 30%) as a fine black powder. The spectral data was identical to that reported.$^{154}$

$^1$H NMR (CDCl$_3$, 300 MHz): 1.29, t, $J = 7.0$ Hz, 3H, OCH$_2$CH$_3$; 2.96, s, 3H, SMe; 4.34, q, $J = 7.0$ Hz, 2H, OCH$_2$CH$_3$; 6.56, s, 1H, CH. $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 14.9, CH$_2$CH$_3$; 29.7, S(CH$_3$)$_2$; 62.0, CH$_2$CH$_3$; 73.7, C$_{60}$sp$^3$C=N; 82.9, C$_{60}$sp$^3$CH; 85.2, CHCO$_2$Et; (134.8; 135.4; 135.9; 136.5; 139.8; 140.7; 140.74; 140.8; 141.98; 142.0; 142.1; 142.14; 142.2; 142.3 (2 x C); 142.4; 142.5 (2 x C); 142.5; 142.53; 142.95; 143.0 (2 x C); 143.04; 143.34; 143.4; 144.44; 144.5; 144.51; 144.6; 145.4; 145.5; 145.57 (2 x C); 145.60, 145.7 (2 x C); 145.78; 145.79; 145.80; 145.9; 146.2; 146.22 (3 x C); 146.4; 146.43; 146.5; 146.6 (2 x C); 146.7; 146.8; 147.4; 147.5; 148.1; 148.4; 149.8; 153.3) C$_{60}$sp$^2$; 170.1, CO; 175.2, CN. ESI-MS (-ve): m/z 879 (100%, M$^+$).

tert-Butyl N-(2,2-dimethylpropylidene)alaninate 172

To a suspension of alanine tert-butyl ester hydrochloride (0.36 g, 2.0 mmol) in anhydrous ethanol (20 mL) were added Et$_3$N (0.20 g, 2.0 mmol) at RT. The mixture was stirred for 10 min before MgSO$_4$ (0.36 g, 3.0 mmol) and pivaldehyde (0.17 g, 2.0 mmol) was added and the mixture was heated at reflux for 3 h. The suspension was filtered and the solution was reduced in vacuo and then redissolved in diethyl ether. The solution was washed with water (3 x 10 mL),
dried (MgSO₄), filtered and concentrated to provide the title compound (0.35 g, 82%) as a clear oil. The spectral data was identical to that reported.¹⁴³ ¹H NMR (CDCl₃, 500 MHz): δ 1.00, s, 9H, CH=NC(CH₃)₃; 1.29, d, J = 6.9 Hz, 3H, CHCH₃; 1.37, s, 9H, CO₂C(CH₃)₃; 3.69, q, J = 6.9 Hz, 1H, CHCH₃; 7.47, s, 1H, CH=N. ¹³C NMR (CDCl₃, 75 MHz): δ 18.8, CH₃; 26.7, C=NC(CH₃)₃; 27.9, CO₂C(CH₃)₃; 36.1, CH=NC(CH₃)₃; 67.9, CH; 80.5, CO₂C(CH₃)₃; 171.7, CO₂; 173.7, CH=N. ESI-MS (+ve): m/z 214 (100%, M+H).

**tert-Butyl 2-methyl-5-tert-butylfulleropyrrolidine 2-carboxylate 173**

To a solution of [60]fullerene (0.086 g, 0.12 mmol) in chlorobenzene (60 mL) was added tert-butyl-N-(2,2-dimethylpropylidene)alaninate (0.051 g, 0.24 mmol) and manganese(III) acetate dihydrate (0.064 g, 0.24 mmol). The solution was heated at reflux under an atmosphere of nitrogen for 8 h. The crude mixture was then subjected to flash silica gel chromatography. Elution with CH₂Cl₂/hexanes (1 : 1) afforded 173 (0.0067 g, 6%) as a dark brown solid. ¹H NMR (CDCl₃, 300 MHz): δ 1.49, s, 9H, CO₂(CH₃)₃; 1.55, s, 9H, CH(CH₃)₃; 2.31, s, 3H, CH₃; 4.36, d, J = 15.2 Hz, 1H, NH; 4.72, d, J = 15.2 Hz, 1H, CH. ESI-MS (-ve): m/z 933 (100%, M⁻).

**tert-Butyl diphenylmethylenealaninate 174**¹⁴³

To a suspension of tert-butyl alaninate hydrochloride (0.36 g, 2.0 mmol) in CH₂Cl₂ (10 mL) was added benzophenone imine (0.36 g, 2.0 mmol). The reaction mixture was stirred vigorously for 24 h before being filtered and then concentrated
Chapter 7: Experimental

under reduced pressure. The yellow oil was then redissolved in diethyl ether (10 mL) and washed with brine (3 x 10 mL). The organic phase was then dried (MgSO₄), filtered and concentrated in vacuo to yield 174 (0.53 g, 86%) as a pale yellow oil. The spectral data was identical to that reported. ¹H NMR (CDCl₃, 500 MHz): δ 1.41, d, J = 6.8 Hz, 3H, CHCH₃; 1.44, s, 9H, C(CH₃)₃; 4.04, q, J = 6.8 Hz, 1H, CHCH₃; 7.18, dd, J = 1.5, 7.3 Hz, 2H, trans-ArH3,5; 7.31, m, 2H, cis-ArH3,5; 7.35, m, 1H, trans-ArH4; 7.43, m, 3H, trans-ArH2,6, cis-ArH4; 7.64, dd, J = 1.5, 7.3 Hz, 2H, cis-ArH2,6. ¹³C NMR (CDCl₃, 75 MHz): δ 19.1, CHCH₃; 28.0, C(CH₃)₃; 61.2, CHCH₃; 80.6, C(CH₃)₃; 127.6, trans-ArC3,5; 127.9, cis-ArC3,5; 128.4, trans-ArC2,6; 128.6, cis-ArC2,6; 130.0, ArC4, 4'; 136.5, trans-ArC1; 139.6, cis-ArC1; 169.2, C=N; 171.9, CO₂. ESI-MS (+ve): m/z 310 (100%, M+H).

Ethyl N-phthalyglycinate 175

To a suspension of ethyl glycinate hydrochloride (0.70 g, 5.0 mmol) and phthalic anhydride (0.74 g, 5.0 mmol) in toluene (20 mL) was added Et₃N (1.5 g, 15 mmol). The mixture was then vigorously heated at reflux under azeotropic conditions for 3 h. The cooled solution was then concentrated in vacuo, redissolved in CH₂Cl₂ and washed with brine (3 x 20 mL). The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure to provide the title compound (1.1 g, 94%) as a crystalline white solid. The spectral data was identical to that reported. m.p.- 108-110 °C lit. m.p. 110. ¹H NMR (CDCl₃, 300 MHz): δ 1.25, t, 3H, J = 7.3 Hz, CH₃; 4.19, q, 2H, CH₂CH₃; 4.40, s, 2H, NCH₂; 7.71, dd, 2H, J = 3.0, 5.5 Hz, ArH4, ArH5; 7.84, dd, 2H, J = 3.0, 5.5 Hz, ArH3, ArH6. ¹³C NMR (CDCl₃, 75 MHz) δ 14.0, CH₃; 38.8, NCH₂; 61.8, CH₂CH₃; 123.5, ArC4, ArC5; 131.9, ArC1, ArC2; 134.1, ArC3, ArC6; 167.1, NCO; 167.4, CO₂.
ESI-MS (+ve) m/z 234 (100%, M+H). This compound was previously characterised by m.p., \(^1\)H NMR and IR and to the best of our knowledge no \(^{13}\)C NMR or MS data has been reported. m.p. - 108-110 °C lit. m.p. 110.\(^{156}\)

\textit{1-Bromoethyl N-phthalylglycinate 176}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{176.png}};
\end{tikzpicture}
\end{center}

To a solution of phthalimide 175 (0.20 g, 0.86 mmol) in carbon tetrachloride (15 mL) was added, N-bromosuccinimide (0.30 g, 1.7 mmol). The mixture was irradiated with a UV lamp for 3 h, and then filtered and the filtrate partitioned with water. The organic phase was collected then concentrated \textit{in vacuo} and the crude material subjected to column chromatography. Elution with CH\(_2\)Cl\(_2\)/hexanes (9 : 1) provided the title compound 176 (0.17 g, 63%) as a yellow solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.93, d, 3H, \(J = 6.0\) Hz, CH\(_3\); 4.46, ABq, 2H, \(J = 17.7\) Hz, CH\(_2\); 6.68, t, 1H, \(J = 6.0\) Hz, CHBr; 7.73, dd, 2H, \(J = 3.0, 5.7\) Hz, ArH\(_4\), ArH\(_5\); 7.87, dd, 2H, \(J = 3.0, 5.7\) Hz, ArH3, ArH6. \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 26.6, CH\(_3\); 38.8, CH\(_2\); 71.7, CHBr; 123.6, ArC4,5; 131.7, ArC1,2; 134.3, ArC3,6; 165.07, NCO; 167.05, CO. ESI-MS (+ve) m/z 313\(^{79}\)Br, 315\(^{81}\)Br (100%, M+H).

\textit{Methyl N-phthalylglycinate 178} \(^{155}\)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{178.png}};
\end{tikzpicture}
\end{center}

To a suspension of methyl glycinate hydrochloride (1.0 g, 8.0 mmol) and phthalic anhydride (1.2 g, 8.0 mmol) in toluene (20 mL) was added Et\(_3\)N (1.8 g, 18 mmol). The mixture was then vigorously heated at reflux under azeotropic conditions for 3 h. The cooled solution was then concentrated \textit{in vacuo}, redissolved in CH\(_2\)Cl\(_2\) and washed with brine (3 x 20 mL). The organic phase was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to provide the title compound 178 (1.6 g, 91%) as a crystalline white solid. \(^1\)H NMR
(CDCl₃, 500 MHz): δ 3.74, s, 3H, CH₃; 4.42, s, 2H, CH₂; 7.72, dd, 2H, J = 3.0, 5.5 Hz, ArH₄, ArH₅; 7.85, dd, 2H, J = 3.0, 5.5 Hz, ArH₃, ArH₆. ¹³C NMR (CDCl₃, 75 MHz) δ 38.6, CH₂; 52.6, CH₃; 123.5, ArC₃,6; 131.9, ArCl₁,2; 134.2, ArC₄,5; 167.3, CO; 167.6, CO. ESI-MS (+ve): m/z 220 (100%, M+H). This compound was previously characterised by m.p., and to the best of our knowledge no NMR data has been reported. m.p.- 112-114 °C lit. m.p. 116.¹⁸¹

Methyl α-bromo-N-phthalylglycinate 179 ¹⁵⁷

To a suspension of 178 (0.20 g, 0.91 mmol) in carbon tetrachloride (20 mL) was added NBS (0.33 g, 1.8 mmol) and the reaction mixture was irradiated with a UV lamp for 10 h. The reaction mixture was stirred at RT for 14 h then more NBS (0.33 g, 1.8 mmol) was added and the reaction mixture was irradiated for 10 h. The solution was then filtered and reduced in vacuo before being subjected to silica gel column chromatography. Elution with CH₂Cl₂/hexanes (1 : 1) provided title compound 179 (0.057 g, 21%) as a white solid. Which was spectroscopically identical to that reported in the literature.¹⁵⁷

¹H NMR (CDCl₃, 500 MHz): δ 3.88, s, 3H, CH₃; 6.68, s, 1H, CHBr; 7.80-8.00, m, 4H, ArH.

Methyl 61-N-phthalimidomethanofullerene 61-carboxylate 180

DBU (0.082 mL, 0.56 mmol) was added at RT to a solution of [60]fullerene (0.10 g, 0.14 mmol) and 179 (0.045 g, 0.15 mmol) in toluene (200 mL). The solution was stirred for 32 h then concentrated in vacuo to approximately half the volume. The crude residue was then subjected to flash silica gel
Chapter 7: Experimental

column chromatography. Elution with CH$_2$Cl$_2$/hexanes (1 : 1) followed by recrystallisation from CH$_2$Cl$_2$/hexane afforded the title compound **180** (0.049 g, 37%) as a fine black powder.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.01, s, 3H, CH$_3$; 7.88, dd, 2H, $J$ = 3.5, 5.0 Hz, ArH3, H6; 8.03, dd, 2H, $J$ = 3.5, 5.0 Hz, ArH4, H5. $^{13}$C NMR (CDCl$_3$/CS$_2$, 2 : 3, 150 MHz): $\delta$ 53.6, CH$_3$; 54.0, CCO$_2$Me; 70.9, C$_{60}$sp$^3$; 124.1, ArC3, 6; 133.7, ArC1, 2; 134.7, ArC4, 5; (136.5, 141.0, 141.1, 141.6, 141.7, 142.0, 142.2, 142.3, 142.6, 142.8 (1/2 x C), 142.9 (1/2 x C), 143.0, 143.1, 143.2, 143.6, 143.8, 144.0, 144.2 (1/2 x C), 144.56, 144.6, 144.61 (1/2 x C), 144.68, 144.7, 144.72, 144.9, 145.1, 145.2 (2 x C), 145.22, 145.6, 145.9) C$_{60}$sp$^2$; 164.5, CO$_2$Me; 166.4, CO. ESI-MS (+ve): $m/z$ 938 (100%, M+H).

1,3-Bis{[(N-diphenylmethylene)acetoxy]methyl}benzene **183**

To a suspension of **187** (0.54 g, 1.1 mmol) in CH$_2$Cl$_2$ (10 mL) was added benzophenone imine (0.45 g, 2.5 mmol) and the reaction was stirred vigorously for 24 h before being filtered and then concentrated under reduced pressure. The yellow residue was dissolved in diethyl ether (50 mL) and washed with brine (3 x 50 mL). The organic phase was dried (MgSO$_4$), concentrated and recrystallised from CH$_2$Cl$_2$ to furnish **183** (0.52 g, 81%) as a white amorphous solid. The spectral data was identical to that reported. $^{108}$ $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 4.25, s, 4H,CH$_2$NCPh$_2$; 5.17, s, 4H, benzylCH$_2$; 7.15, m, 4H, ArH; 7.32, m, 8H, ArH; 7.43, m, 8H, ArH; 7.65, dd, 4H, $J$ = 8.3, 1.3 Hz, ArH. $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 55.5, NCH$_2$; 66.2, benzylCH$_2$; 127.5, transArC3,5; 128.0, cisArC3,5; 128.1, benzylArC4,6; 128.6, transArC2,6; 128.7, cisArC2,6; 128.75, benzylArC5; 128.8, benzylArC2; 130.5, cis and transArC4; 135.8, transArC1; 136.0, benzylArC1,3; 139.1, cisArC1; 170.4, CN; 172.0, CO. ESI-MS (+ve): 581 (100%, M+H).
1,4-Bis\{[(N-diphenylmethylidene)acetoxy]methyl\}benzene 184\(^{108}\)

To a suspension of 188 (8.6 g, 18 mmol) in DCM (20 mL) was added benzophenone imine (6.5 g, 36 mmol) and the reaction mixture was stirred vigorously for 24 h before being filtered and concentrated \textit{in vacuo}. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic phase was dried (MgSO\(_4\)) and concentrated \textit{in vacuo} and recrystallised from diethyl ether to yield 184 (7.6 g, 73\%) as a white amorphous solid. The spectral data was identical to that reported.\(^{108}\)\(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 4.17, s, 4H, CH\(_2\)NCPh\(_2\); 5.09, s, 4H, benzylCH\(_2\); 7.13, m, 8H, ArH; 7.35, m, 4H, ArH; 7.39, m, 4H, ArH; 7.42, m, 4H, ArH; 7.64, dd, 4H, \(J = 8.4, 1.6\) Hz, ArH. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 55.5; 66.0; 127.9; 128.1; 128.6; 129.9; 132.3; 137.4; 170.3; 172.0. ESI-MS (+ve): 581 (100\%, M+H).

1,3-Bis\{[(N-tert-butoxycarbonyl)acetoxy]methyl\}benzene 185\(^{108}\)

To a solution of 1,3-benzenedimethanol (0.50 g, 3.6 mmol), \textit{N}-tert-butoxycarbonylglycine (1.3 g, 7.4 mmol) and DMAP (0.15 g, 1.2 mmol) in THF (10 mL) was added DCC (1.6 g, 7.8 mmol). The mixture was stirred for 40 h, filtered and then concentrated \textit{in vacuo}. The crude residue was redissolved in CH\(_2\)Cl\(_2\) (15 mL) and washed sequentially with HCl (0.1M, 5 mL), Na\(_2\)CO\(_3\) (0.1M, 5 mL) and brine (5 mL). The organic phase was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure and the residue was subjected to column chromatography. Elution with CH\(_2\)Cl\(_2{/}\)methanol (49 : 1) afforded 185 (1.2 g, 76\%) as a light yellow oil. The spectral data was identical to that reported.\(^{109}\) \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.44, s, 18H,
(CH₃)₃; 3.96, d, 2H, J = 5.7 Hz, CH₂NHBOC; 5.10, bs, 2H, NH; 5.18, s, benzylCH₂; 7.34, m, 4H, ArH. ¹³C NMR (CDCl₃, 75 MHz): δ 28.2, CH₃; 42.4, NCH₂; 66.6, benzylCH₂; 80.0, C(CH₃)₃; 128.1, ArC4,6; 128.3, ArC2; 128.9, ArC5; 135.7, ArC1,3; 155.7, CO₂C(CH₃)₃; 170.2, CO₂CH₂. ESI-MS (+ve): m/z 453 (100%, M+H).

1,4-Bis[(N-tert-butoxycarbonyl)acetoxymethyl]benzene 186¹⁰⁹

To a solution of 1,4-benzenedimethanol (5.0 g, 36 mmol), N-tert-butoxycarbonyl glycine (12.6 g, 71.9 mmol) and DMAP (0.88 g, 7.2 mmol) in THF (20 mL) was added DCC (15.6 g, 75.5 mmol). The mixture was stirred for 40 h, filtered and then concentrated in vacuo. The crude residue was redissolved in CH₂Cl₂ (15 mL) and washed sequentially with HCl (0.1M, 5 mL), Na₂CO₃ (0.1M, 5 mL) and brine (5 mL). The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure and the residue was subjected to column chromatography. Elution with CH₂Cl₂/methanol (49:1) afforded 186 (14.3 g, 86%) as a white solid. The spectral data was identical to that reported.¹⁰⁹ ¹H NMR (CDCl₃, 300 MHz): δ 1.42, s, 18H, (CH₃)₃; 3.91, bd, 4H, J = 5.2 Hz, CH₂NHBOC; 5.12, bs, 2H, NH; 5.14, s, 4H, benzylCH₂; 7.33, s, 4H, ArH. ¹³C NMR (CDCl₃, 75 MHz): δ 28.1, CH₃; 42.2, NCH₂; 64.5, benzylCH₂; 79.7, C(CH₃)₃; 127.3, ArC2,3,5,6; 132.3, ArC1,4; 156.1, CO₂C(CH₃)₃; 170.2, CO₂CH₂. ESI-MS (+ve): m/z 453 (100%, M+H).

1,3-Bis[acetoxymethylglycinate]benzene.bistrifluoroacetate salt 187¹⁰⁹

The ester 185 (0.60 g, 1.3 mmol) was added to neat TFA (2.0 mL) and the mixture stirred for 1 h before being concentrated under reduced pressure. The reaction mixture
was redissolved in distilled water (10 mL) and washed with diethyl ether (3 x 10 mL). The aqueous phase was retained and freeze-dried overnight to provide 187 (0.54 g, 86%) as a colourless oil. The spectral data was identical to that reported.\(^{109}\) \(^1\)H NMR (D\(_2\)O, 300 MHz): \(\delta\) 3.95, s, 4H, CH\(_2\)N; 5.30, s, 4H, benzyl CH\(_2\); 7.47, m, 4H, ArH. ESI-MS (+ve): \(m/z\) 480 (100%, M\(^+\)).

1,4-Bis[acetoxyethylglycinate]benzene.bistrifluoroacetate salt 188 \(^{109}\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NH}_2\cdot\text{TFA} & \quad \text{NH}_2\cdot\text{TFA} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

The ester 186 (14.3 g, 31.6 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 h and then concentrated \textit{in vacuo}. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous phase was retained and freeze-dried overnight to yield 188 (13.6 g, 90%) as a colourless oil. The spectral data was identical to that reported.\(^{109}\) \(^1\)H NMR (D\(_2\)O, 500 MHz): \(\delta\) 3.81, s, 4H, CH\(_2\)N; 5.21, s, 4H, benzyl CH\(_2\); 7.31, s, 4H, ArH. ESI-MS (+ve): \(m/z\) 480 (100%, M\(^+\)).

\textit{trans-4} \textit{m}-Phenylenedimethyl bis-5,5-diphenyfullerenylidihydropyrrole 2,2'-dicarboxylate 189 and \textit{cis-3} \textit{m}-Phenylenedimethyl bis-5,5-diphenyfullerenylidihydropyrrole 2,2'-dicarboxylate 190 \(^{109}\)

DBU (0.11 mL, 0.75 mmol) was added at RT to a solution of [60]fullerene (0.11 g, 0.15 mmol), carbon tetrabromide (0.14 g, 0.36 mmol) and 183 (0.12 g, 0.21 mmol) in toluene (200 mL). The solution was stirred for 3 h then washed with NH\(_4\)Cl (50 mL) then brine (50 mL), dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo} to approximately half the volume. The mixture was then filtered through a short plug of flash silica gel. Elution with toluene removed the
unreacted [60]fullerene, elution with CH$_2$Cl$_2$ provided 189 and 190 as a mixture. Column chromatography of the crude residue CH$_2$Cl$_2$/hexanes (9 : 1) and recrystallisation from CH$_2$Cl$_2$/diethyl ether provided 189 (0.062 g, 32%) as a brown solid. The spectral data was identical to that reported.$^{109}$ $^1$H NMR (CDCl$_3$, 300 MHz): 189: δ 5.06, d, 2H, $J=11.2$ Hz, CHH; 5.71, d, 2H, $J=11.2$ Hz, CHH; 7.07, t, 1H, $J=7.6$ Hz, ArH; 7.14, s, 1H, ArH; 7.30, t, 2H, $J=7.6$ Hz, ArH; 7.40, t, 4H, $J=7.2$ Hz, ArH; 7.46, t, 4H, $J=7.2$ Hz, ArH; 7.55, t, 4H, $J=7.2$ Hz, ArH; 7.92, d, 4H, $J=8.4$ Hz, ArH; 8.04, d, 4H, $J=8.4$ Hz, ArH. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 68.0, 81.5, 81.8, 97.1, 127.9, 128.0, 128.3, 129.4, 129.6, 136.4, 137.7, 138.9, 139.6, 140.6, 140.9, 141.3, 141.33, 141.4, 141.5, 142.1, 142.5 (ipso), 143.6, 143.9, 145.6, 145.7, 145.75, 145.80, 146.0, 146.03 (1/2 x C), 146.7, 146.8, 146.82, 147.4, 148.6, 149.0 (1/2 x C), 149.9, 150.9, 160.7, 161.3. ESI-MS (-ve): $m/z$ 1296 (100%, M$^-$).

Further elution with CH$_2$Cl$_2$/hexanes (9 : 1) afforded 190 (0.018 g, 9%) as a brown solid. The spectral data was identical to that reported.$^{109}$ 190: $^1$H NMR (CDCl$_3$, 300 MHz): δ 5.31, d, 2H, $J=11.2$ Hz, CHH; 5.41, d, 2H, $J=11.2$ Hz, CHH; 6.95, s, 1H, ArH; 7.18, m, 3H, ArH; 7.23, t, 4H, $J=7.6$ Hz, ArH; 7.37, dd, 4H, $J=7.2$ Hz, 1.6 Hz, ArH; 7.50, dd, 4H, $J=7.6$ Hz, 1.2 Hz, ArH; 7.62, t, 4H, $J=8.4$ Hz, ArH; 8.17, d, 4H, $J=7.6$ Hz, ArH; 8.21, d, 4H, $J=7.6$ Hz, ArH. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 68.5, 81.8, 82.4, 96.0, 128.3, 128.6, 129.6, 129.9, 131.4, 134.6, 134.8, 138.5, 139.2, 140.7, 141.0, 141.2, 141.8, 143.4, 143.5, 144.0, 144.1, 144.11, 144.3, 144.4, 144.7, 144.9, 145.0, 145.9 (1/2 x C), 147.3, 147.4, 147.5, 147.8, 148.6, 148.9, 149.0, 149.2, 150.9, 153.4, 154.4, 161.0, 161.1. ESI-MS (-ve): $m/z$ 1296 (100%, M$^-$).
**Chapter 7: Experimental**

*trans-3 p*-Phenylenedimethyl bis-5,5-diphenylfullerenyldihydropyrrole 2,2’-dicarboxylate 191 and *trans-4 p*-Phenylenedimethyl bis-5,5-diphenylfullerenyldihydropyrrole 2,2’-dicarboxylate 192

DBU (0.11 mL, 0.75 mmol) was added at RT to a solution of [60]fullerene (0.11 g, 0.15 mmol), carbon tetrabromide (0.14 g, 0.36 mmol) and 183 (0.12 g, 0.21 mmol) in toluene (200 mL). The solution was stirred for 3 h then washed with NH₄Cl (50 mL) then brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to approximately half the volume. The mixture was then filtered through a short plug of flash silica gel. Elution with toluene removed the unreacted [60]fullerene, elution with CH₂Cl₂ provided 191 and 192 as a mixture. Column chromatography of the crude residue CH₂Cl₂/hexanes (9 : 1) and recrystallisation from CH₂Cl₂/diethyl ether provided 191 (0.072 g, 37%) as a brown solid. 191: The spectral data was identical to that reported.¹⁰⁹ ¹H NMR (CDCl₃/CS₂, 6 : 4, 300 MHz): δ 5.21, d, 2H, J = 11.6 Hz, CHH; 5.58, d, 2H, J = 11.6 Hz, CHH; 7.16, d, 2H, J = 4.4 Hz, ArH; 7.39, d, 2H, J = 4.4 Hz, ArH; 7.51, m, 8H, ArH; 7.62, t, 4H, J = 7.2 Hz, ArH; 8.16, d, 4H, J = 7.2 Hz, ArH; 8.21, d, 4H, J = 7.2 Hz, ArH. ¹³C NMR (CDCl₃, 125 MHz): too insoluble to obtain adequate spectrum. ESI-MS (-ve): m/z 1296 (100%, M⁻).

Further elution with CH₂Cl₂/hexanes (9 : 1) afforded 191 (0.019 g, 10%) as a brown solid. 191: The spectral data was identical to that reported.¹⁰⁹ ¹H NMR (CDCl₃/CS₂, 6 : 4, 300 MHz): δ 5.17, d, 2H, J = 14.4 Hz, CHH; 5.72, d, 2H, J = 14.4 Hz, CHH; 7.29, m, 4H, ArH; 7.40, m, 4H, ArH; 7.46, t, 4H, J = 10.0 Hz, 1.6 Hz, ArH; 7.55, t, 4H, J = 9.6 Hz, ArH; 7.92, d, 4H, J = 9.6 Hz, ArH; 8.02, d, 4H, J = 9.6 Hz, ArH. ¹³C NMR (CDCl₃/CS₂, 6:4, 75 MHz): δ 67.9, 86.8, 83.0, 96.7, 128.1, 128.2, 128.4, 129.6, 129.7, 134.2, 135.6, 136.2, 137.3, 138.4, 139.8, 140.7, 141.2, 141.5, 144.0, 144.1, 145.5,
Chapter 7: Experimental

145.8, 146.0, 146.8, 146.9, 147.4, 147.6, 148.9, 150.3, 151.0, 160.7, 161.3. ESI-MS (-ve): m/z 1296 (100%, M⁻).

3-Hydroxymethylbenzyl 5,5-diphenylfullerenyldihydropyrrole-2-carboxylate 193

DBU (2.2 mL, 15 mmol) was added at RT to a solution of [60] fullerene (1.1 g, 1.5 mmol), carbon tetrabromide (1.4 g, 3.6 mmol) and 183 (1.2 g, 2.1 mmol) in o-dichlorobenzene (300 mL). The solution was stirred for 2 h then washed with NH₄Cl (100 mL) then brine (100 mL), dried (MgSO₄), filtered and applied directly to silica gel column. Elution with CH₂Cl₂ provided a mixture of 189/190 (2 : 1) 18%, further elution with CH₂Cl₂ provided 193 (0.32 g, 20%) as a brown solid. ¹H NMR (CDCl₃/CS₂ (1 : 1), 500 MHz): δ 4.63, s, 2H, CH₂OH; 5.52, s, 2H, CH₂; 7.38, m, 4H, ArH; 7.47, m, 6H, ArH; 8.05, d, 4H, J= Hz, ArH. ¹³C NMR (CDCl₃/CS₂ (1:1), 125 MHz): 64.8, CH₂OH; 68.1, CH₂; 82.7, 2 x C₆₀ sp³; 95.9, NCP₂; 127.0, ArC; 127.1, ArC; 127.8, ArC; 128.3, ArC; 128.4, ArC; 128.9, ArC; 129.6, ArC; (134.6, 134.8, 136.6, 139.1, 139.6, 140.8, 141.2, 141.7) C₆₀ sp²; 141.75, ArCl, Cl¹; (142.2, 142.3, 142.6, 142.7, 142.9, 144.07, 144.1, 144.8, 145.0, 145.03, 145.3 (2 x C), 145.35, 145.7, 145.85, 145.9, 146.3, 146.8 (1/2 x C), 147.0 (1/2 x C), 147.4, 148.3, 153.0) C₆₀ sp²; 160.1 C=N; 161.8, C=O. ESI-MS (-ve): m/z 1077 (100%, M⁻).
Chapter 7: Experimental

*m*-Phenylenedimethyl trans-4 bis-[diphenylmethylamino-α(-1,9-dihydrofullerenyI)-2,2'-dicarboxylate] 196 and
1,3-Bis[([N'-diphenylmethylaminoacetoxy]methyl)-2''-(1',9''-dihydrofullerenyI)benzene 195

Boron trifluoride diethyl etherate (0.057 g, 0.40 mmol) was added dropwise over 1 min to a solution of 189 (0.050 g, 39 µmol) in THF (30 mL) at -78 °C under an atmosphere of argon. The reaction mixture was stirred for 10 min then sodium cyanoborohydride (0.025 g, 0.40 mmol) and glacial acetic acid (0.1 mL) were added to the reaction mixture, which was stirred for 15 min at -78 °C before CH₂Cl₂ (50 mL) was then added and the reaction mixture was quenched with ice water. The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure (at 0 °C) then, subjected to flash silica gel chromatography. Elution with CH₂Cl₂/hexanes (3 : 2), afforded the title compound 196 (0.0043 g, 8.5%) as a brown amorphous solid. ¹H NMR (CDCl₃, 300 MHz): δ 3.21, d, 1H, J = 13.8 Hz, NH; 3.52, d, 1H, J = 13.5 Hz, NH; 4.53, d, 1H, J = 13.5 Hz, CHPh; 4.57, d, 1H, J = 11.1 Hz, OCH₂; 4.62, d, 1H, J = 13.8 Hz, CHPh; 4.66, d, 1H, J = 11.7 Hz, OCH₂; 5.16, s, 1H, NCHCO₂; 5.24, s, 1H, NCHCO₂; 5.50, d, 1H, J = 11.7 Hz, OCH₂; 5.76, d, 1H, J = 11.1 Hz, OCH₂; 6.24, s, 1H, C₆₀H; 6.61, s, 1H, C₆₀H; 6.78, d, 1H, J = 8.0 Hz, ArH; 6.96, m, 3H, ArH; 7.16, d, 1H, J = 8.0 Hz, ArH; 7.33, t, 2H, J = 7.3 Hz, ArH; 7.45, m, 6H, ArH; 7.58, m, 3H, ArH; 7.65, d, 2H, J = 7.0 Hz, ArH; 7.72, d, 2H, J = 7.0 Hz, ArH; 7.80, d, 2H, J = 7.0 Hz, ArH; 7.88, d, 2H, J = 7.0 Hz, ArH. ESI-MS (-ve): m/z 1303 (100%, M-H).
Further elution with CH$_2$Cl$_2$/hexanes (7 : 3) provided 195 (0.031 g, 62%) as a brown solid. The spectral data was identical to that reported.$^{109}$ 195: $^1$H NMR (CDCl$_3$/CS$_2$, 80:40, 600 MHz): $\delta$ 3.37, s, 2H, H$_g$; 3.66, dd, 1H, $J =$ 12.3, 2.7 Hz, NH$_b$; 4.84, s, 1H, H$_h$; 4.98, d, 1H, $J =$ 12.3 Hz, H$_d$; 5.07, s, 2H, H$_e$; 5.24, d, 1H, $J =$ 11.9 Hz, H$_d$/H$_d'$; 5.28, d, 1H, $J =$ 2.7 Hz, H$_c$; 5.41, d, 1H, $J =$ 11.9 Hz, H$_d$/H$_d'$; 6.84, s, 1H, C$_{60}$H; 7.20, m, 10H, ArH; 7.30, m, 8H, ArH; 7.41, t, 2H, $J =$ 7.9 Hz, ArH; 7.47, t, 2H, $J =$ 7.6 Hz, ArH; 7.64, d, 2H, $J =$ 7.8 Hz, ArH; 7.74, d, 2H, $J =$ 7.8 Hz, ArH. $^{13}$C NMR (CDCl$_3$/CS$_2$ (80:40), 150 MHz): $\delta$ 49.1, 58.9, 66.1, 66.4, 66.6, 67.3, 67.7, 70.4, 127.25, 127.3, 127.7, 128.0, 128.7, 128.9, 129.0, 129.1, 129.12, 129.3, 135.5, 136.1, 136.3, 136.4, 137.3, 139.2, 139.6, 140.37, 140.4, 141.47, 141.5, 141.54, 141.7, 141.72, 142.0, 142.04, 142.06, 142.1, 142.14, 142.2, 142.4, 142.56, 142.58, 142.6, 143.1, 143.13, 143.2, 144.3, 144.4, 144.7, 144.74, 145.2, 145.3, 145.35 (2 x C), 145.4, 145.44, 145.6, 145.7, 145.8, 145.9, 146.16, 146.18, 146.2, 146.25, 146.3, 146.38, 146.4, 146.43, 146.5, 147.0, 147.1, 147.2, 147.5, 151.1, 151.2, 153.0, 154.0, 172.3, 172.4. ESI-MS(+ve): m/z 1327 (100%, M+Na).

1,3-Bis{[(N-diphenylmethyl)acetoxy]methyl}benzene 198

To a solution of 1,3-bis{[(N-diphenylmethylidene)acetoxy]methyl}benzene 183 (0.050 g, 0.086 mmol) in CH$_2$Cl$_2$ (20 mL) was added sodium cyanoborohydride (0.020 g, 0.32 mmol). The mixture was then stirred vigorously for 16 h under an atmosphere of nitrogen before being
concentrated under reduced pressure and then subjected to column chromatography. Elution with CH$_2$Cl$_2$/hexanes (7 : 3) furnished 198 as a white powder (0.023 g, 46%). The compound has been reported in the literature however no data (spectral or otherwise) was provided.$^{108,109}$ $^1$H NMR (CDCl$_3$, 300 MHz): δ 2.33, bs, 1H, NH; 3.42, s, 2H, CH$_2$NH; 4.87, s, 1H, CHPh$_2$; 5.15, s, 2H, benzylCH$_2$; 7.25, m, 7H, ArH; 7.35, m, 3H, ArH. $^{13}$C NMR (CDCl$_3$, 75MHz): 49.0, NHCH$_2$; 66.1, CHPh$_2$; 66.5, benzylCH$_2$; 127.0, ArC2; 127.2, ArC4, 6; 127.3, ArC4',4''; 128.5, ArC3',3'',5',5''; 128.6, ArC2',2''',6',6''; 129.3, ArC5; 135.8, ArCl1,3; 143.1, ArCl1',1''; 172.4, CO. ESI-MS (+ve): m/z 585 (100%, M+H).

Diethyl trans-4 bis-(5,5-diphenylfullerenyldihydropyrrole)-2,2'-dicarboxylate 199

Solid potassium carbonate (0.50 g, 4.7 mmol) was added to a solution of 189 (0.20 g, 0.15 mmol) in THF : EtOH (2 : 1, 100 mL) and the mixture was stirred at RT for 2 h. The mixture was then filtered and the solvent removed in vacuo. The crude residue was subjected to flash silica gel column chromatography. Elution with CH$_2$Cl$_2$ provided 199 (0.16 g, 83%) as a brown amorphous solid. The spectral data was identical to that reported.$^{109}$ $^1$H NMR (300 MHz, CDCl$_3$): δ 1.41, t, 6H, J = 6.8 Hz, CH$_3$; 4.48, q, 4H, J = 6.8 Hz, CH$_2$; 7.29, t, 4H, J = 7.2 Hz, ArH; 7.38, t, 4H, J = 8.0 Hz, ArH; 7.46, t, 4H, J = 7.2 Hz, ArH; 7.56, t, 4H, J = 8.0 Hz, ArH; 7.90, dd, 2H, J = 7.2 Hz, 1.2 Hz, ArH; 8.06, dd, 2H, J = 7.6 Hz, 1.2 Hz, ArH. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 14.2, 63.0, 81.5, 82.0, 96.6, 128.1, 128.2, 128.4, 129.6, 129.8, 131.4, 134.0, 136.6, 136.8, 139.0, 140.1, 140.7, 140.8, 141.4, 141.6, 141.9, 142.0 (2 x C), 142.3, 143.9, 145.7, 145.75, 145.8, 146.0,
146.4, 146.4, 146.7, 146.8 (2 x C), 147.2, 147.6, 147.8, 148.7 (2 x C), 148.8, 150.1, 151.0 (2 x C), 151.4, 160.5, 162.2. ESI-MS (+ve): \( m/z \) 1250 (100%, \( M^+* \)).

Diethyl cis-3 bis-(5,5-diphenylfullerenylidihydropyrrole)-2,2'-dicarboxylate 200

Solid potassium carbonate (0.50 g, 4.7 mmol) was added to a solution of 190 (0.20 g, 0.15 mmol) in THF : EtOH (2 : 1) (100 mL) and the mixture was stirred at RT for 2 h. The mixture was then filtered and the solvent was removed \textit{in vacuo}. The crude residue was then subjected to column chromatography. Elution with \( \text{CH}_2\text{Cl}_2 \) followed by recrystallisation (chloroform/diethyl ether) delivered 200 (0.15 g, 81%) as a brown amorphous solid. The spectral data was identical to that reported.\(^{109}\) \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 1.42, t, 6H, \( J = 8.0 \text{ Hz}, \text{CH}_3\); 4.48, q, 4H, \( J = 8.0 \text{ Hz}, \text{CH}_2\); 7.36, t, 4H, \( J = 8.0 \text{ Hz}, \text{ArH}\); 7.49, m, 4H, ArH; 7.63, t, 4H, \( J = 8.0 \text{ Hz}, \text{ArH}\); 8.09, d, 4H, \( J = 8.0 \text{ Hz}, \text{ArH}\); 8.25, d, 4H, \( J = 8.0 \text{ Hz}, \text{ArH}\). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta \) 17.1, 62.4, 68.1, 81.9, 82.4, 95.9, 128.3, 128.5, 128.8, 129.9, 130.1, 131.0, 135.0, 136.3, 138.5, 139.3, 140.5, 140.8, 141.1, 141.5, 141.9, 142.4, 143.4, 143.9, 143.91, 144.2, 144.5, 144.9, 145.1, 145.3, 145.6, 147.4, 147.8, 147.9, 147.95, 148.57, 148.6, 148.7, 148.73, 151.4, 153.6, 154.2, 160.5, 162.2, 167.8. ESI-MS (+ve): \( m/z \) 1250 (100%, \( M^+* \)).
Diethyl cis-3 bis-(diphenylmethylamino-\(\alpha\)-1,9-dihydrofullerenyl glycinate) 201a and 201b and 99a

Boron trifluoride-diethyl etherate (0.057 g, 0.40 mmol) was added dropwise over 1 min to a solution of 200 (0.050 g, 40 \(\mu\)mol) in THF (30 mL) at -78 °C under an atmosphere of argon. The reaction mixture was stirred for 10 min then sodium cyanoborohydride (0.025 g, 0.40 mmol) and glacial acetic acid (0.1 mL) were added to the reaction mixture, which was stirred for 15 min at -78 °C. CH\(_2\)Cl\(_2\) (50 mL) was then added and the reaction mixture quenched with ice/water. The organic phase was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure (at 0 °C) then subjected to flash silica gel chromatography. Elution with CH\(_2\)Cl\(_2\)/hexanes (3 : 2), afforded a mixture of the title compound 201 (0.0063 g, 13%), as a 1 : 1 mixture of isomers (201a and 201b), and the known dihydrofullerene 99a (0.020 g, 51%), as determined by \(^1\)H NMR. 201a: \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.48, d, 2H, \(J = 12.0\) Hz, NH\(_D\); 4.20, m, 8H*, 2 x CH\(_2\)CH\(_3\); 4.59, d, 2H, \(J = 12.5\) Hz, H\(_B\); 5.13, bs, 4H*, H\(_C\); 6.52, s, 2H, H\(_A\). 201b: \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.28, app.dd, 2H, \(J = 12.0, 3.3\) Hz, NH\(_{dd'}\); 4.20, m, 8H*, 2 x CH\(_2\)CH\(_3\); 4.63, d, 1H, \(J = 12.0\) Hz, H\(_{b/b'}\); 4.64, d, 1H, \(J = 12.0\) Hz, H\(_{b'/b}\); 5.13, bs, 4H*, H\(_C\) and H\(_{e/e'}\); 6.51, s, 1H, H\(_{a/a'}\); 6.518, s, 1H, H\(_{a'/a}\). ESI-MS (+ve): \(m/z\) 990 (100%, 99a+H). * Indicates resonance overlap between diastereomers.

trans-4 Bis-(5,5-diphenylfullerylidihydropyrrole-2-carboxylic acid) 202
To a vigorously stirred solution of 189 (0.100 g, 0.077 mmol) in CH₂Cl₂ (100 mL) at −10 °C was added BBr₃ (0.400 g, 1.6 mmol) dropwise. The mixture was then left for 15 h at RT, before slowly adding water (50 mL) to quench the excess reactant. The organic phase was separated, dried (MgSO₄), filtered and reduced in vacuo. The crude residue was then redissolved in chloroform and precipitated out using hexane to provide the title compound 202 (0.053 g, 58%) as a brown amorphous solid. ¹H NMR (300 MHz, CDCl₃): δ 7.28, t, 1H, J = 7.2 Hz, ArH4; 7.39, t, 2H, J = 7.2 Hz, ArH3,5; 7.46, t, 1H, J = 7.2 Hz, ArH4; 7.56, t, 2H, J = 7.2 Hz, ArH3',5'; 7.94, d, 2H, J = 7.2 Hz, ArH2,6; 8.08, d, 2H, J = 7.2 Hz, ArH2',6'; 8.71, bs, 1H, CO₂H. ESI-MS (-ve): m/z 1192 (100%, M⁻), 1148 (M - CO₂), 720 (C₆₀), 596 (M²⁻).

trans-4 Bis-(methyl 2-[5',5'-diphenylfullerenyldihydropyrrole-(2S)-2-carboxamido]-3-phenylpropanoate) 203

To a solution of 202 (0.080 g, 0.067 mmol) in CH₂Cl₂ (50 mL) was added HOBt (0.020 g, 0.150 mmol) and EDCI (0.029 g, 0.150 mmol) and the mixture was stirred for 15 min before a solution of L-phenylalanine methyl ester hydrochloride (0.032 g, 0.15 mmol) and Et₃N (0.020 g, 0.20 mmol) in CH₂Cl₂ (5 mL) was added dropwise. The resulting solution was stirred at RT for a further 3 h before the solvent was removed under reduced pressure. The crude residue was then subjected to flash silica chromatography. Elution with CH₂Cl₂ provided the title compound 203 (0.056g, 56%) as a brown solid. ¹H NMR (CDCl₃, 500 MHz): δ 3.16, dd, 2H, J = 13.5, 6.0 Hz, CH₃Ph; 3.26, dd, 1H, J = 13.5, 6.0 Hz, CHHPh; 3.32, dd, 1H,
Chapter 7: Experimental

\[ J = 13.5, 6.0 \text{ Hz, CH}_2^\text{Ph}; 3.73, s, 3\text{H, CH}_3; 3.75, s, 3\text{H, CH}_3; 5.01, m, 2\text{H, 2 x CH};
7.11, m, 2\text{H, ArH}; 7.17, m, 3\text{H, ArH}; 7.22, m, 4\text{H, ArH}; 7.29, m, 2\text{H, ArH}; 7.38, m, 4\text{H, ArH};
7.45, m, 4\text{H, ArH}; 7.54, m, 4\text{H, ArH}; 7.54, d, 2\text{H, } J = 8.5 \text{ Hz, ArH}; 7.85, d, 2\text{H, } J =
7.5 \text{ Hz, ArH}; 7.97, m, 5\text{H, ArH}, 2 \times \text{NH}. \]

\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)}: \delta 38.0, \text{CH}_2; 38.2, \text{CH}_2; 52.7, 2 \times \text{CH}; 53.4, \text{CH}_3; 53.5, \text{CH}_3; 80.9, 2 \times \text{C}_{60}\text{sp}^3; 82.6, \text{C}_{60}\text{sp}^3; 82.7,
\text{C}_{60}\text{sp}^3; 96.1, \text{C}_{60}\text{sp}^2; 96.2, \text{C}_{60}\text{sp}^2; (127.36, 127.4, 128.2, 128.3, 128.4, 128.5, 128.6,
128.8, 129.5, 129.53, 129.6, 129.7, 129.8, 129.85) \text{ArC's}; (131.1, 131.3, 134.4, 134.5)
\text{C}_{60}\text{sp}^2; 135.6, \text{benzyl ArC1}; 135.65, \text{benzyl ArC1'}; (136.65, 136.7, 136.8, 136.9, 139.0,
139.1, 140.0, 140.05, 140.9, 141.0, 141.15, 141.2, 141.5, 141.55) \text{C}_{60}\text{sp}^2; 146.0,
\text{diphenylC1, C1', C1'', C1'''}; (141.95, (2 x C), 142.0, 142.1, 142.3, 142.4, 144.0, 144.1,
145.85, 145.9, 146.0 (2 x C), 146.1, 146.2 (2 x C), 146.5, 146.7, 146.75, 146.8, 146.85,
146.9, 147.1, 147.3, 147.5, 147.7 (2 x C), 147.8, 147.85, 148.5, 148.6, 148.9, 149.0,
149.05, 150.0, 150.2, 151.1, 151.2, 151.4) \text{C}_{60}\text{sp}^2; 160.4, \text{C=NN}; 160.45, \text{C=NN}; 162.0
\text{CONH}; 162.1, \text{CONH}; 171.3, \text{CO}; 171.5, \text{CO}. \text{ESI-MS (+ve): } m/z 1518 (100%,
\text{M+Na}^+).

*trans*-4 Bis-(ethyl 2-[5',5'-diphenylfullerenyldihydropyrrole-(2S)-2-carboxamido]-3-
phenylpropanoate) 204

To a solution of 202 (0.050 g, 0.042 mmol) in CH$_2$Cl$_2$ (30 mL) was added HOBT (0.014 g, 0.10
mmol) and EDCI (0.020g, 0.10 mmol) and the mixture was stirred for 15 min before a solution of L-
phenylalanine ethyl ester hydrochloride (0.023g, 0.10 mmol) and Et$_3$N (0.010g, 0.10 mmol) in CH$_2$Cl$_2$ (2
mL) was added dropwise. The resulting solution was stirred at RT for a further 3 h
before the solvent was removed under reduced pressure. The crude residue was then
subjected to flash silica chromatography, elution with CH₂Cl₂ provided the title compound 204 (0.029 g, 58%) as brown solid. ¹H NMR (CDCl₃, 300 MHz): δ 1.22, m, 6H, CH₃; 3.25, m, 4H, CH₂Ph; 4.20, m, 4H, OCH₂; 4.96, m, 2H, NHCH; 7.13, m, 2H, ArH; 7.19, m, 3H, ArH; 7.22, m, 4H, ArH; 7.30-7.45, m, 10H, ArH; 7.54, m, 4H, ArH; 7.54, d, 2H, J = 8.5 Hz, ArH; 7.85, d, 2H, J = 7.5 Hz, ArH; 7.97, m, 5H, ArH, 2 x NH. ESI-MS (+ve): m/z 1525 (100%, M+H).

2-Ethyl 3-hydroxymethylbenzyl trans-4-bis-(5,5-diphenylfullerenyldihydropyrrole-2-carboxylate) 205

Solid sodium carbonate (0.21 g, 1.5 mmol) was added to a solution of 189 (0.17 g, 0.13 mmol) in THF/EtOH (3 : 1, 100 mL) and the mixture was stirred at RT for 1 h. The mixture was then filtered and the solvent was removed in vacuo. The crude residue was then subjected to column chromatography, elution with CH₂Cl₂ provided the starting material 189 (0.087 g, 51%). Further elution with CH₂Cl₂ provided 205 (0.072 g, 41%) as brown amorphous solid. ¹H NMR (300 MHz, CDCl₃): δ 1.44, t, 3H, J = 6.9 Hz, CH₃; 2.14, t, 1H, J = 6.0 Hz, OH; 4.50, q, 2H, J = 6.9 Hz, CH₂CH₃; 4.59, d, 2H, J = 6.0 Hz, CH₂OH; 5.43, s, 2H, benzylicH₂; 7.29, m, 5H, ArH; 7.37, m, 5H, ArH; 7.45, m, 2H, ArH; 7.55, m, 4H, ArH; 7.88, m, 4H, ArH; 8.05, m, 4H, ArH. ¹³C NMR (75 MHz, CDCl₃): δ 14.2, CH₃; 63.2, CH₂CH₃; 64.6, CH₂OH; 68.3, CO₂CH₂; (81.45, 81.5, 82.1, 82.15) C₆₀sp³; 96.6, CPh₂; 96.7, CPh₂; (127.0, 127.1, 127.8, 128.3, 128.4, 128.8, 129.6, 129.7, 129.8) ArC; (131.5, 131.55, 134.0, 134.05) C₆₀sp²; 134.7, CO₂benzylicArCl; (136.6 (2 x C), 136.8, 136.85, 139.0 (2 x C), 140.1 (2 x C), 140.7 (2 x C), 140.75 (2 x C), 140.8 (2 x C), 140.9 (2 x C), 141.45 (2 x C), 141.5, 141.6 (2 x C), 141.7) C₆₀sp²; 141.9, diphenyl ipso; 142.0, C₆₀sp²;
Chapter 7: Experimental

142.3, diphenyl ipso; 144.0, benzylArC3; (145.6, 145.7, 145.8, 145.85 (2 x C), 146.0 (3 x C), 146.2, 146.45, 146.5, 146.6 (2 x C), 146.7, 146.75, 147.3 (2 x C), 147.6 (2 x C), 147.7, 147.8, 148.8, 148.9 (2 x C), 150.1 (2 x C), 151.1, 151.5 (2 x C)) C_{60}sp^2; 160.4, C=N; 160.6, C=N; 162.0, CO; 162.4, CO. ESI-MS (+ve): 1343 (100%, M+H).

*Ethyl (3-((3-ethoxy-3-oxopropanoyloxy)methyl)benzyloxy) trans-4-bis-(5,5-diphenylfullerenylidihydropyrrole-2-carboxylate) 206*

Ethyl malonyl chloride (0.030 g, 0.20 mmol) was added dropwise to a solution of the alcohol 205 (0.20 g, 0.15 mmol) and pyridine (0.016 g, 0.20 mmol) at 0 °C in CH₂Cl₂ (10 mL). The solution was warmed to RT over 1 h, before the solution was quenched with water (10 mL). The organic phase was separated, washed with saturated aqueous Na₂CO₃ (3 x 10 mL), dried (MgSO₄), filtered and then applied directly to a silica gel column. Elution with CH₂Cl₂ provided the title compound (0.20 g, 91%) as a brown solid. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 1.22, t, 3H, \(J = 7.2\) Hz, malOCH₂CH₃; 1.43, t, 3H, \(J = 7.2\) Hz, diphOCH₂CH₃; 3.38, s, 2H, malCH₂; 4.17, q, 2H, \(J = 7.2\) Hz, malOCH₂CH₃; 4.49, q, 2H, \(J = 7.2\) Hz, diphOCH₂CH₃; 5.14, s, 2H, CH₂CO₂CH₂CO₂Et; 5.44, ABq, 2H, \(J = 15\) Hz, NCO₂CH₂; 7.27-7.40, m, 10H, ArH; 7.46, m, 2H, ArH; 7.89, m, 4H, orthoArH; 8.05, m, 4H, orthoArH. \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta\) 14.2, CH₃; 14.3, CH₃; 41.7, COCH₂CO; 61.7, malOCH₂CH₃; 63.1, diphenylOCH₂CH₃; 66.9, malbenzylCH₂; 68.0, diphenylbenzylCH₂; (81.6, 81.65, 82.15, 82.2) C_{60}sp³; 96.8, 2 x CPh₂; (128.3, 128.4, 128.5, 128.6, 128.7, 129.1) ArC; (131.5, 131.6, 134.1, 134.15) C_{60}sp²; 135.1, benzylArCl; (135.9 (2 x C), 136.65, 136.7, 137.0 (2 x C), 139.1 (2 x C), 140.2 (2 x C), 140.8 (2 x C), 140.85 (2 x C), 140.9 (2 x C), 141.0 (2 x C), 141.5, 141.55

235
(2 x C), 141.6, 141.7 (2 x C) C\textsubscript{60}sp\textsuperscript{2}; 142.0, diphenyl ipso; 142.1, C\textsubscript{60}sp\textsuperscript{2}; 142.4, diphenyl ipso; 144.1, benzylArC3; (145.7, 145.8, 145.85, 145.9 (2 x C), 146.1 (3 x C), 146.3, 146.6, 146.7, 146.75, 146.8, 147.4 (2 x C), 147.7 (2 x C), 147.8, 148.0, 148.9, 148.95, 149.0, 150.1, 150.2, 151.2, 151.5, 151.6) C\textsubscript{60}sp\textsuperscript{2}; 160.5, C=N; 160.6, C=N; 162.1, CO; 162.3, CO; 166.4, malCO; 166.45, malCO. ESI-MS (+ve): m/z 1455 (100%, M+H).

2-Ethyl 3′′-[ethoxycarbonyl(acetoxymethyl)]phenyl-61′′-methanofullerenyl trans-4-bis-(5,5-diphenylfullerenyldihydropyrrole- 2-carboxylate) \textbf{207a} and \textbf{207b}

DBU (0.023 mL, 0.15 mmol) was added at RT to a solution containing \textbf{206} (0.100 g, 0.069 mmol) and carbon tetrabromide (0.023 g, 0.070 mmol) in toluene (200 mL). The solution was stirred for 14 h then concentrated \textit{in vacuo} to approximately half the volume.

The crude residue was subjected to flash silica gel chromatography and elution with CH\textsubscript{2}Cl\textsubscript{2} delivered \textbf{207a} (0.0020 g, 2.0%) as a brown solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.47, m, 6H, CH\textsubscript{3}; 4.48, m, 4H, CH\textsubscript{2}CH\textsubscript{3}; 4.78, d, 1H, \(J = 11.5\) Hz, benzylicCH\textsubscript{H}; 5.31, d, 1H, \(J = 11.5\) Hz, benzylicCH\textsubscript{H}; 5.42, d, 1H, \(J = 11.5\) Hz, benzylicCH\textsubscript{H}; 5.53, d, 1H, \(J = 11.5\) Hz, benzylicCH\textsubscript{H}; 7.40, m, 12H, ArH; 7.53, m, 4H, ArH; 7.90, d, 2H, \(J = 7.5\) Hz, ArH; 7.93, d, 2H, \(J = 7.5\) Hz, ArH; 7.99, d, 2H, \(J = 7.5\) Hz, ArH; 8.05, d, 2H, \(J = 7.5\) Hz, ArH. ESI-MS (+ve): m/z 1453 (100%, M+H).

Further elution with CH\textsubscript{2}Cl\textsubscript{2} provided \textbf{207b} (0.0066 g, 6.6%) as a brown solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.51, app.t, 6H, \(J = 7.5\) Hz, CH\textsubscript{3}; 4.57, q, 2H, \(J = 7.5\) Hz, CH\textsubscript{2}CH\textsubscript{3}; 4.59, q, 2H, \(J = 7.5\) Hz, CH\textsubscript{2}CH\textsubscript{3}; 4.87, q, 1H, \(J = 10.5\) Hz, benzylicCH\textsubscript{H}; 5.04, q, 1H, \(J = 10.5\) Hz, benzylicCH\textsubscript{H}; 5.64, q, 1H, \(J = 10.5\) Hz, benzylicCH\textsubscript{H}; 5.77,
q, 1H, J = 10.5 Hz, benzylicCHH; 7.29-7.47, m, 14H, ArH; 7.58, t, 2H, J = 7.5 Hz, ArH; 7.68, m, 2H, ArH; 7.76, d, 2H, J = 8.0 Hz, ArH; 7.79, d, 2H, J = 8.0 Hz, ArH; 8.07, d, 2H, J = 7.5 Hz, ArH. $^{13}$C NMR (125 MHz, CDCl$_3$): δ 14.3, CH$_3$; 14.4, CH$_3$; 63.0, CH$_2$CH$_3$; 63.2, CH$_2$CH$_3$; 67.6, benzylicCHH; 67.9, benzylicCHH; 78.0, C$_{60}$sp$^3$; 81.5, C$_{60}$sp$^3$; 86.9, C$_{60}$sp$^3$; 96.3, CPh$_2$; 96.3, CPh$_2$; 128.1, 128.3, 128.4, 128.5, 128.9, 129.5, 129.6, 129.7, 129.9, 131.0, 131.3, 133.9, 134.1, 135.14, 135.18, 135.8, 138.9, 139.8, 140.2, 140.9, 141.0, 141.6, 142.3, 144.0, 144.1, 144.2, 144.3, 144.4, 148.3, 148.9, 149.4, 153.2, 160.6, CN; 161.5, CN; 161.9, CO; 162.9, CO, 163.1, CO, 164.1, CO. ESI-MS (+ve): $m/z$ 1453 (100%, M+H).

1,3-Bis[(N-tert-butylidene)acetoxy)methyl]benzene 210

To a suspension of 187 (0.50 g, 1.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added Et$_3$N (0.11 g, 1.0 mmol) at RT. The mixture was stirred for 10 min before MgSO$_4$ (0.48 g, 4.0 mmol) and pivaldehyde (0.17 g, 2.0 mmol) was added and the mixture stirred for 16 h. The suspension was filtered, washed with water (3 x 20 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to provide the title compound (0.26 g, 67%) as a colourless oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.10, s, 18H, (CH$_3$)$_3$; 4.20, s, 4H, NCH$_2$; 5.17, s, 4H, benzylicCH$_2$; 7.34, m, 4H, ArH; 7.57, s, 2H, CH=N. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 26.6, (CH$_3$)$_3$; 36.5, C(CH$_3$)$_3$; 61.4, benzylicCH$_2$; 66.1, NCH$_2$; 127.9, ArC5; 128.0, ArC4, ArC6; 128.8, ArC2; 136.0, ArC1, ArC3; 169.9, CO; 177.2, C=N. ESI-MS (+ve): $m/z$ 389 (100%, M+H). HR ESI-MS (+ve): $m/z$ calculated for (M+H) C$_{22}$H$_{33}$N$_2$O$_4$: 389.2440, found 389.2446.

1-tert-Butylidene-3-amino-1,3-bis(acetoxymethyl)benzene 212
To a suspension of 187 (0.50 g, 1.0 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (0.11 g, 1.0 mmol) at RT. The mixture was stirred for 10 min before MgSO₄ (0.48 g, 4.0 mmol) and pivaldehyde (0.085 g, 1.0 mmol) was added and the mixture stirred overnight. The suspension was filtered, washed with water (3 x 20 mL), dried (MgSO₄), filtered and concentrated in vacuo to provide the title compound (0.21 g, 66%) as a colourless oil. ¹H NMR (CDCl₃, 500 MHz): δ 1.10, s, 9H, (CH₃)₃; 3.48, s, 2H, NH₂CH₂; 4.20, s, 2H, CH₂N; 5.16, s, 2H, benzylCH₂; 5.18, s, 2H, benzylCH₂; 7.31, m, 4H, ArH; 7.57, s, 1H, CH=NH. ESI-MS (+ve): 321 (100%, M+H).

**m-Phenylendimethyl bis-(5,5-tert-butylfulleropyrrolidine-2-carboxylate) 213**

DBU (0.300 g, 2.0 mmol) was added at RT to a solution containing [60]fullerene (0.40 g, 0.56 mmol) and 210 (0.22 g, 0.56 mmol) in chlorobenzene (200 mL). The solution was stirred for 12 h then filtered through a short plug of flash silica gel with CH₂Cl₂. The crude residue was further purified via flash silica gel chromatography. Gradient elution using CH₂Cl₂/hexanes (7 : 3 to 9 : 1) followed by preparative thin phase chromatography (CH₂Cl₂) provided the title compound 213 (0.018 g, 2.9%) as brown solid. Trans-trans ¹H NMR (CDCl₃, 300 MHz): δ 1.71, s, 18H, CH₃; 4.55, s, 2H, (CH₃)₃CCH; 4.99, d, 2H, J = 11.4 Hz, benzylCHH; 5.26, s, 2H, CHCO₂; 5.27, d, 2H, J = 11.4 Hz, CHH; 6.77, s, 1H, Ar2; 7.13, t, 1H, J = 7.3 Hz, Ar5; 7.36, d, 2H, J = 7.3 Hz, Ar4,6. ¹³C NMR (CDCl₃, 75 MHz): δ 29.8, CH₃; 36.2, C(CH₃)₃; 67.4, CH₂; 71.5, CHC(CH₃)₃; 77.5, C₆₀sp³; 82.7, CHCO₂; 128.7, ArC₂; 131.9, ArC₄, 6; 132.0, ArC₅; 133.9, ArCl, 3; (135.6; 136.8; 138.6; 140.1; 141.1; 141.3; 141.4; 141.7; 143.46; 143.5;
143.68; 143.7; 144.4; 144.8; 145.2; 145.4; 146.8; 147.9; 148.1; (1/2 x C), 148.25; 148.3, (1/2 x C); 148.5; 148.7; 148.9; 149.5; 149.8, (1/2 x C); 150.0; 152.7; 155.1; 157.3) C_{60}sp^2; 169.1 CO. *Another C_{60}sp^3 resonance was expected and was speculated to occur at the same chemical shift as the deuterated chloroform. Additionally one half-intensity resonance was not observed and was thought to be obscured by a full-intensity resonance). ESI-MS (-ve): m/z 1108 (100%, M^*).
Chapter 8: References

8. References


APPENDIX

ESI-MS data for Chapter 5, isotopic ratio refers to the ratio of M, M+1, M+2 etc. Species refers to the molecular ion species (radical anion, M⁻ Vs deprotonation (M-H)).

**MSMS data**

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Appendix

Ethyl ester methanofullerene 222

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|                                 | 908            | 28.5     | 47       | 46       |
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### Appendix

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